Christine Ludwig

Effects of daily bitter gourd consumption for 2 months among pre-diabetics;

an intervention trial in Moshi, Tanzania

DISSERTATION
submitted to the Faculty of Agricultural Sciences,
Nutritional Sciences, and Environmental Management
Justus Liebig University Giessen
for the degree of Dr. oec. troph.

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Faculty of Agricultural Sciences, Nutritional Sciences, and Environmental Management
Institute of Nutritional Sciences
Professor for International Nutrition
Justus Liebig University Giessen, Germany

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INAUGURAL-DISSERTATION

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By

Christine Ludwig, M. Sc.
Born in Gehrden, Germany

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Examination Committee:

Referee: Prof. Dr. med. Michael B. Krawinkel

1st Co-referee: Prof. Dr. med. Thomas Linn

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Examiner: Prof. Dr. Ernst August Nuppenau

Examiner: Prof. Dr. Gunter P. Eckert

Examiner: Prof. Dr. Monika Neuhäuser-Berthold

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Abbreviations

ADA	American Diabetes Association
AHA	American Heart Association
AVRDC	Asian Vegetable Research and Development Center (World Vegetable Center)
BMI	Body mass index
BP	Blood pressure
Chol	Cholesterol
FFQ	Food frequency questionnaire
FPG	Fasting plasma glucose
GPT	Glutamate-pyruvate transaminase
HbA_{1c}	Glycated hemoglobin
HDL	High-density lipoprotein
HOMA	Homeostasis model assessment
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
KCMC	Kilimanjaro Christian Medical Centre
KCRI	Kilimanjaro Clinical Research Institute
NIMR	National Institute for Medical Research
OAD	Oral anti-diabetic drugs
OGTT	Oral glucose tolerance test
PAQ	Physical activity questionnaire
PPAR	Peroxisome proliferator-activated receptor
RBG	Random blood glucose
TFDA	Tanzanian Food and Drug Authority
TG	Triglycerides
UKPDS	United Kingdom Prospective Diabetes Study
WC	Waist circumference
WHO	World Health Organization

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Chapter 1: Introduction

This dissertation is divided into three chapters. Chapter 1 provides the rationale for and background information on the dietary intervention study conducted in Moshi, Tanzania, 2013/14. This study was part of the project "A better bitter gourd: Exploiting bitter gourd to increase incomes, manage type 2 diabetes, and promote health in developing countries" which was coordinated by the AVRDC-The World Vegetable Center in Taiwan. Chapter 2 includes information on a cross-sectional survey which was conducted as part of the bitter gourd project in 2011 among diabetic patients in the same research area. Chapter 3 and following sections describes the intervention study and its recruitment procedure followed by their discussion.

1.1 Emerging epidemic of pre-diabetes and diabetes in low- and middle-income countries

Some non-communicable diseases such as type 2 diabetes mellitus type, are major health problems, not only in high-income, but also in low- and middle-income countries (WHO 2014). Type 2 diabetes mellitus is a disease which is partially linked to overweight and obesity as well as to low physical activity (Popkin *et al.* 2012; WHO 2014; Go *et al.* 2013; Boutayeb *et al.* 2005). Numbers of people living with diabetes are high and expected to further increase within the next decades (Figure 1).

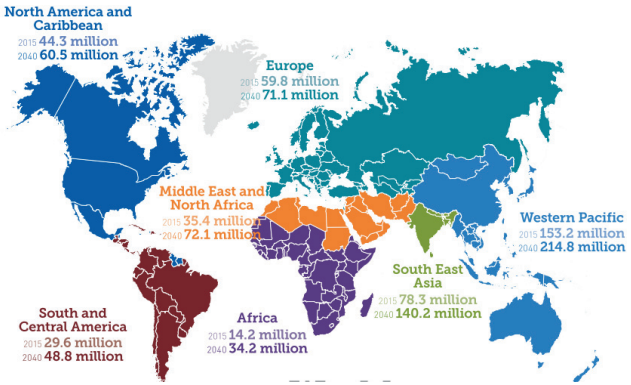


Figure 1 Estimated number of people (20-79 years) with diabetes per region in 2015 and 2040 (IDF 2015)

Diabetes is defined as fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL) or 2-h plasma glucose ≥11.1mmol/l (200mg/dl) (WHO *et al.* 2006). In the age group of 20-79 years, the current estimate of the global prevalence of diabetes is 8.8%, with an expected increase to 10.4% by 2040. In Sub-Saharan Africa, the current estimate of the regional prevalence is 3.2% with an expected increase to 4.2% by 2040. It is assumed that almost 67% of diabetes cases are still undiagnosed in this region (IDF 2015). In Sub-Saharan Africa, including the United Republic of Tanzania, 90% of all cases are type 2 diabetes mellitus (Levitt 2008). The International Diabetes Federation (IDF) estimated Tanzania's national diabetes prevalence to be 2.3% in 2011 (IDF 2012), 7.8% in 2013 (IDF 2013), and 3.5% in 2015 (IDF 2015). Other studies showed diabetes rates ranging from 0.6% to 5.8% (Kavishe *et al.* 2015; Aspray *et al.* 2000). Prevalence of pre-diabetes, defined as impaired glucose tolerance (IGT), were 10.6% in 2011 (IDF 2012) and 9.1% in 2013 (IDF 2013).

1.2 Pre-diabetes

Pre-diabetes refers to a dysglycemic state which lies between normal glucose regulation and diabetes (Perreault *et al.* 2014). Pre-diabetic states are mostly defined according to FPG and 2-h glucose concentrations and are categorized into isolated impaired fasting glucose (IFG), isolated IGT, or combined IFG and IGT. Cut-off values for IGT are 7.8-11.0 mmol/L (140-199 mg/dL) for 2-hour glucose levels measured during an oral glucose tolerance test (OGTT) with a 75 g glucose load (WHO 1999; ADA 2010). Different cut-off values are used to define isolated IFG. Values recommended by the World Health Organization (WHO) are 6.0-6.9 mmol/L (WHO *et al.* 2006) and those recommended by the American Diabetes Association (ADA) are 5.6-6.9 mmol/L (ADA 2010). The ADA also recommends the use of HbA_{1c} to define pre-diabetes with cut-off values of 5.7-6.4% (39-46 mmol/mol) (ADA 2010). Metabolic defects such as insulin resistance, beta cell dysfunction, and ectopic fat accumulation which lead to IFG or IGT and can further progress to type 2 diabetes mellitus are presented in Table 1, p.13 (Perreault *et al.* 2014).

Table 1 Metabolic defects in impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Perreault *et al.* 2014)

	Isolated IFG	Isolated IGT	Combined IFG and IGT
Insulin resistance			
Reduced peripheral glucose disposal (Abdul-Ghani *et al.* 2008; Ahrén *et al.* 1997; Færch *et al.* 2009; Kantartzis *et al.* 2010; Li *et al.* 2013; van der Zijl *et al.* 2010)	–	+	++
Increased hepatic glucose production (Abdul-Ghani *et al.* 2008; Kantartzis *et al.* 2010; Li *et al.* 2013; Perreault *et al.* 2010; van der Zijl *et al.* 2010)	+	–	+
Beta cell dysfunction			
Defective absolute insulin secretion (Abdul-Ghani *et al.* 2008; Li *et al.* 2013; van der Zijl *et al.* 2010)	+	–	++
Defective relative insulin secretion (Fritsche *et al.* 2000; Laakso *et al.* 2007; Li *et al.* 2013; Nauck *et al.* 2010; van der Zijl *et al.* 2010)	+	++	++
Ectopic fat accumulation			
Increased fat content in the liver (Alssema *et al.* 2013; Henkel *et al.* 2005)	+	++	+++
Increased fat content in skeletal muscle (Vollmer *et al.* 2008)	+	+	+

"+" and "–" indicate whether the condition is present in the different pre-diabetic subtypes in relation to individuals with normal glucose regulation. The number of "+" and "–" indicate the severity of the conditions

Pre-diabetes can be detected during a screening at clinical visits or public screening activities in communities. Different screening methods may be applied individually or in combination, depending on the purpose and scope of the screening. Such methods include questionnaires, measurement of FPG, random blood glucose (RBG), HbA_{1c}, or conduction of an OGTT test. A screening can be performed in stages, starting, for example, with using a questionnaire to assess risk factors, followed by an assessment of the glycemic status of those with elevated risk factor scores. The ADA recommends a screening every three years for asymptomatic adults older than 45 years of age and for younger adults with a BMI ≥25 kg/m² who have at least one additional risk factor such as physical inactivity or a first-degree family member with diabetes (ADA 2014). However, some argue that screening for diabetes mellitus and pre-diabetes is not justifiable (Diabetes Care 2002), as it does not meet all criteria for disease screening (National Cancer Control Policy Australia 2015; Wilson, J. M.G. *et al.* 1968).

Although pre-diabetes does not always progress to type 2 diabetes mellitus, up to 25% of cases do so within three years after diagnosis (Nichols *et al.* 2007). In Tanzania, the management and treatment possibilities for diabetes are insufficient (Ministry of Health and Social Welfare, Tanzania 2013; Peck *et al.* 2014a; Robertson *et al.* 2015). Thus, prevention of diabetes is one way to reduce the socioeconomic burden that arises from increases in prevalence and uncontrolled diabetes (Wyne 2008). In addition to lifestyle interventions, which have been shown to positively influence glucose metabolism (Jenkins *et al.* 2011; Samjoo *et al.* 2013), medicinal plants with anti-diabetic properties (Khan *et al.* 2012; Parikh *et al.* 2014; Tag *et al.* 2012; Yakubu *et al.* 2015) might be used to lower raising blood glucose levels and, thus, to prevent or delay the onset of diabetes.

1.3 Phytomedicine: *Momordica charantia*

In regard to the increasing rates of diabetes mellitus and pre-diabetes as well as lack of sufficient diabetes care described in chapter 1.2, alternative strategies to lower glucose levels and to prevent or delay the onset of diabetes may be explored. One alternative strategy to medical treatment is the use of plants with hypoglycemic properties (Grover *et al.* 2002; Joseph *et al.* 2013; Wang *et al.* 2013). *Momordica charantia* (Figure 2, p. 15), also known as bitter gourd, bitter melon, or balsam pear is a flowering vine pre-dominantly cultivated in Asian countries, but also available in African and South-American countries. In East Africa, it is mainly collected from the wild It belongs to the family of *Cucurbitacae,* has both female and male flowers, green leaves, and edible fruits which exhibit a bitter taste (Basch *et al.* 2003; Grover *et al.* 2004; Krawinkel *et al.* 2006). Unripe fruits can vary in size and color from white to dark green. Ripe fruits are inedible (Sathishsekar *et al.* 2005; Alam *et al.* 2015).

Figure 2 Bitter gourd plant grown in a private garden (left) and bitter gourd fruits purchased from the local center market an supermarket in Moshi

Bitter gourd includes high amounts of vitamin A, C, E, B1, B2, B3, and folate. Further it includes high amounts of calcium, zinc, iron, and fiber, among others. Other compounds of bitter gourd which are also responsible for its bitter taste are phenols, terpenes such as saponins, and glucosinolates (RI *et al.* 2006; Snee *et al.* 2011). Bitter gourd has not only been used for its hypoglycemic properties, but also against cancer, malaria, ulcer, dyslipidemia, and hypertension (Alam *et al.* 2015) with its anti-inflammatory, antiviral, and antibacterial properties (Budrat *et al.* 2008; Joseph *et al.* 2013).

Anti-diabetic effects of extracts and isolated compounds of bitter gourd have been demonstrated in many animal studies in type one and type two diabetic rodents (Klomann *et al.* 2010; Huang *et al.* 2008; Huang *et al.* 2013; Sridhar *et al.* 2008). Several human studies which have been conducted to assess hypoglycemic effects of bitter gourd supplementation resulted in different outcomes (Tongia *et al.* 2004; Dans *et al.* 2007; John *et al.* 2003; Zänker *et al.* 2012; Srivastava *et al.* 1993; Tsai *et al.* 2012; Welihinda *et al.* 1986; Fuangchan *et al.* 2011; Kochhar *et al.* 2011) and no clear recommendation on the application of bitter gourd variety, dosage, and mean of consumption could be made. However, usage of whole raw fruits may exhibit the highest potential of hypoglycemic effects (Habicht *et al.* 2014). The hypoglycemic effect of bitter gourd may be more of short term rather than cumulative (Platel *et al.* 1997)

1.4 Objectives

The main objective of the intervention study was to examine anti-diabetic effects of 2.5 g dried bitter gourd powder per day over the course of eight weeks among pre-diabetic study participants. The study aimed to examine differences between bitter gourd and placebo treatment in regard to FPG as the primary outcome. Detailed information on hypothesis and secondary outcomes is provided in chapter 3.1

Chapter 2: Knowledge of bitter gourd and diabetes among diabetic patients in the Kilimanjaro Region, Tanzania

2.1 Introduction

Increasing diabetes prevalence implies increasing diabetes-related complications, including macro- and microvascular diseases such as retinopathy, foot ulcers, and nephropathy, as well as coronary heart problems (Fowler 2008). In a 2003 review, African populations were reported to have low rates of macrovascular disease, but the highest rates of microvascular diseases, compared to other populations. Microvascular complications might be linked to poor glycemic control due to inadequate access to, or high costs of, medical care, and late diagnosis of diabetes (Mbanya *et al.* 2003; Gill *et al.* 2008; Justin-Temu *et al.* 2009). Chiwanga and Njelekela (2015) found that among diabetic patients in a setting in Dar es Salaam, 15% had foot ulcers, 44% had peripheral neuropathy, and 15% had peripheral vascular disease. Forty-eight percent of the patients had received education on foot care, mostly from nurses (Chiwanga *et al.* 2015). Limited knowledge of diabetes among communities, diabetic patients, and health professionals was found in studies across the globe (Chiwanga *et al.* 2015; Sircar *et al.* 2010; Metta *et al.* 2015; Sweileh *et al.* 2014; Kavishe *et al.* 2015; Guler *et al.* 2011). The current study aimed to assess knowledge of bitter gourd as an anti-diabetic plant as well as knowledge, burden, and management of diabetes among diabetic patients in the Kilimanjaro Region in Tanzania.

2.2 Methods

2.2.1 Study area

The study was conducted in June and July 2011 at the diabetes clinics of the Kilimanjaro Christian Medical Centre (KCMC) in Moshi and the Machame Lutheran Hospital (MLH) in the Hai District. Both are located in the Kilimanjaro Region in northern Tanzania, which had a population of 1,640,087 people in 2012 (National Bureau of Statistics & Ministry of Finance 2013). Moshi Municipality is the capital of the region and had 184,292 inhabitants in 2012. Machame is located approximately 15 km from Moshi Municipality on the slope of Mt. Kilimanjaro and had a population of about 67,000 in 2012 (National Bureau of Statistics, Ministry of Finance, *et al.* 2013; Machame Lutheran Hospital 2015b). Machame Lutheran Hospital is owned by the Evangelical Lutheran Church of Tanzania-Northern Diocese. The hospital serves a catchment area of the approximately 1.6 million people of the Kilimanjaro Region and has more than 22,000 outpatients per year. After malaria, diabetes is the second most common disease treated in the hospital (Machame Lutheran Hospital 2015b; Machame Lutheran Hospital 2009; Machame Lutheran Hospital 2015a). Kilimanjaro Christian Medical Centre is one of the four referral hospitals of Tanzania and serves a catchment area of approximately 11 million people in Northern Tanzania. KCMC has had a diabetes clinic since 1996, which was visited by about 2,000 adult and 370 pediatric patients in 2014. There were three trained staff members, one examination room, and one consultation room (Kilimanjaro Christian Medical Centre 2015b; Kilimanjaro Christian Medical Centre 2015a).

2.2.2 Objectives

The objectives of this study were to assess knowledge on and usage of bitter gourd, bitter plants and phytomedicine among diabetic patients. It further aimed to assess knowledge, burden, and management of diabetes among the diabetic patients. The findings of this study will be used to suggest future interventions and research topics regarding diabetes in the region.

2.2.3 Study design and recruitment

The current study was a cross-sectional survey. Adult patients were recruited through convenience sampling during clinic visits. Patients were informed on the purpose and procedure of the study prior to their regular checkup and asked to participate in this survey. At KCMC, patients came on Wednesdays and Fridays for regular checkups, during which nurses measured FPG, blood pressure (BP), and body weight. Medical counseling by a physician was offered on Wednesdays. At MLH, opening hours were on Tuesdays. Inclusion criteria were being over the age of 18 years, being a registered diabetic patient, and giving consent to participate in the study. This study was explorative, so no sample size calculation was applied.

2.2.4 Data collection

Standardized questionnaires with structured, semi-structured, and open-ended questions were administered in private areas of the hospitals by trained nurses in face-to-face interviews in Swahili, Tanzania's national language (Figure 3, p. 19). Questionnaires were compiled in English forward and backward translated, and pre-tested among diabetic patients at KCMC. English versions of the questionnaires are given in the appendix (A-C). Demographic and socioeconomic status were recorded, along with age at diagnosis, type, family history, burden, management, and knowledge of diabetes. The burden of diabetes was assessed using open-ended questions in which patients were asked about complications and whether they had to give up something to pay for treatment. Management of diabetes was assessed with open-ended questions about the type of treatment and frequency of visits to a doctor. Knowledge was assessed using open-ended questions about symptoms, complications, and causes of diabetes. Data on body weight and height were obtained from the medical files of the participants. Body mass index (BMI, kg/m^2) was categorized by the following cut-off points: <18.5 (underweight), 18.5-24.9 (normal weight), 25.0-29.9 (overweight), 30.0-34.9 (obese class I), 35.0-39.9 (obese class II), and ≥40.0 (obese class III) (WHO 2015; WHO 2004).

Figure 3 Interview setting; patients were shown pictures of bitter gourd to be able to recognize the fruit

2.2.5 Statistics

Data analysis was performed using SPSS versions 20 and 22 (SPSS Inc, Chicago Illinois). Results are expressed as average values, with mean and standard deviation (SD) used if data are consistent with a normal distribution and median and interquartile range (IQR) used if data are not consistent with a normal distribution, or as frequencies. A knowledge score was calculated for each participant from the total number of correctly named symptoms, complications, and causes. Scores were categorized using percentile ranges to represent little (5^{th}-25^{th}), medium (25^{th}-50^{th}), good (50^{th}-90^{th}), and very good (above 90^{th}) knowledge. Differences were calculated for sex, insurant or non-insurant, farmer or non-farmer, and member or non-member of a diabetes support group. The two-sample t-test was used to compare means of normally distributed variables and the Mann-Whitney U-test was used to compare non-normally distributed continuous data. Categorical data was tested with the chi-squared test. Effect size was calculated using Rosenthal's r. Correlations between variables were calculated using Spearman's rho. In all statistical tests, $p<0.05$ was considered statistically significant.

2.2.6 Ethical considerations

Ethical clearance was obtained from the Institutional Review Board of Kilimanjaro Christian Medical College. Further approval was obtained from the regional medical officer. Verbal consent was obtained from each participant prior to the interview, after explaining the

procedure and purpose of the study. Each participant was informed that he or she could withdraw at any time without consequences.

2.3 Results

2.3.1 Demographic and anthropometric profile of diabetic patients

A total of 155 patients (53% female) were interviewed, all of African origin. Demographic and socioeconomic details of the participants are shown in Table 2, p.21. Median age was 57.0 (46.8-65.0) years. The majority of patients were married and had at least primary education. The occupation varied between the patients. However, the plurality was a farmer or did farm field services. Males were older than females (Mdn=62.0 vs. Mdn=54.0, U=2159.5, z=-2.885, p=0.004, r=-0.232). Thirty-four percent of participants were farmers. Educational level was similar between sexes but was higher among farmers than non-farmers (Mdn=3 vs. Mdn=5, U=1717, z=-3.431, p=0.001, r=-0.277).

Mean BMI was higher among females (M±SD=27.8±5.0, SE: 0.56 kg/m²) than males (M±SD=25.5±3.4, SE: 0.40 kg/m²), (t(153)=3.335, p=0.001, r=0.26). In addition, BMI categories differed between sexes, with females having a higher prevalence in the obese categories (U=2235, z=-2.908, p=0.004, r=-0.234). There was no significant difference in BMI between farmers and non-farmers. BMI was positively correlated with age at diagnosis (rho=0.226, p<0.001). BMI classification for female, male, and all participants is shown in Figure 4.

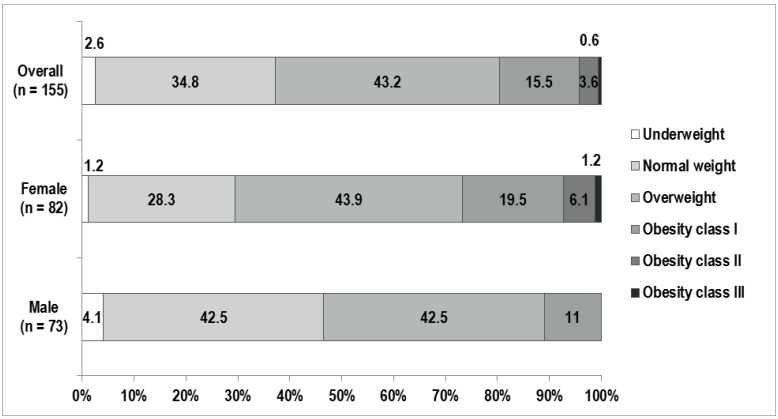


Figure 4 Distribution of BMI of overall, female, and male participants

Table 2 Demographic and socioeconomic data of participants

Variable	n	Overall	Female	Male
Age in years	154	57.0	54.0	62.0
[median, IQR]		(46.8 – 65.0)	(42.5 – 62.0)	49.5 – 69.0)
Age in years at diagnosis	152	46.0	45.0	49.5
[median, IQR]		(36.3 – 55.0)	(35.0 – 53.0)	(37.0 – 57-0)
Body mass index [mean±SD]	155	26.74±4.5	27.8±5.0	25.5±3.4
Marital status [%]	154			
Single		18	17	18
Married		64	54	74
Separated/divorced		2	4	0
Widowed		17	25	8
Religion [%]	155			
Christian		82	88	75
Islam		18	12	25
Educational level [%]	155			
No formal		2	2	1
Few years primary		21	23	19
Completed primary		26	33	19
Few years secondary		7	5	8
Completed secondary		8	5	12
High school/still studying		36	32	40
Occupational status [%]	155			
Artisan		4	2	5
Business sector		14	12	16
Farmer or farm labor service		34	35	32
Housewife		6	11	0
Service industry		10	7	14
Student		5	5	5
Teacher		14	21	7
Retired		9	1	18
Other		4	7	3

2.3.2 Knowledge and usage of bitter gourd among diabetic patients

Only 7% have ever heard of bitter gourd**,** usually from neighbors, friends, or family members. Four percent did state they used bitter gourd to treat a disease, but did not further specify the disease. If bitter gourd was eaten, it was mainly consumed daily as juice, boiled, or cooked and mixed with other vegetables and purchased at the market. One patient of the pre-test specified the preparation of bitter gourd she was using for her diabetes. She squeezed the plant and mixed the juice with water and drank two cups per day. Of those who know bitter gourd, the majority have heard that bitter gourd is used to treat diabetes, while one patient had heard of its effect on hypertension. None of the patient stated to eat bitter gourd as a usual vegetable. Bitter gourd season could not be detected within this survey. However, bitter plants were consumed 90% of participants and around 50% said to know and use medicinal plants. A total of 21 bitter plants and 44 medicinal plants were named. Most consumed bitter vegetables were hare lettuce and African nightshade. Most named treated diseases were hypertension, diabetes, cancer, and wounds. Almost all patients would eat specific vegetables with anti-diabetic effects, and would both grow them in their garden or purchase them.

2.3.3 Individual burden of diabetes

Median age at diagnosis was 46 years (36.3-55.0), with no significant difference between sexes. Farmers were older at diagnosis than non-farmers (Mdn=53.5 vs. Mdn=44.0, U=1717, z=-3.431, p=0.001, r=-0.275). The median number of years living with diabetes since diagnosis was 8.0 (36.3-55), and was higher among males than females (Mdn=9.0 vs. Mdn=7.5, U=2263.5, z=-2.389, p=0.017, r=-0.193).

Table 3 on p.23, shows symptoms perceived before diagnosis and current reported complications. The duration with which patients had symptoms before diagnosis ranged from one week (10%) to over ten years (1%). One patient perceived symptoms during pregnancy. Around 40% perceived symptoms between six months and one year prior to diagnosis. When patients were asked who else in their family had diabetes, 41% said a first-degree relative, 5% said a second-degree relative, 6% said both, and 3% said a spouse. Among the 28 participants who had to give up something to pay for medication and checkups, only seven were NHIF

members or received donations. Patients reported having to forego expensive clothing, luxurious or healthy food, and traveling to afford diabetic care.

Table 3 Perceived symptoms of diabetic patients prior to diagnosis and reported complications

Symptoms [%]	Overall (n=155)	Complications [%]	Overall (n=155)
Frequent urination	87.7	Impaired sight	11.6
Thirst	87.7	Blindness	4.5
Weakness and fatigues	92.3	Impotence	8.4
Tingling and/or numbness	68.4	Numbness	5.8
Weight loss	4.5	Amputation	1.3
Blurred vision	3.2	Hypertension	42.6

2.3.4 Knowledge on diabetes

Eight percent of patients knew they were type I diabetic, 17% knew they were type II diabetic, and 75% did not know their diabetes type. At least one symptom, complication, or possible cause could be named by 92%, 76%, and 45% of patients, respectively. Knowledge scores ranged from 0 to 11. Patients were categorized into groups having no or little knowledge (15%), medium knowledge (31%), good knowledge (44%), and very good knowledge (10%). Knowledge scores and categories did not differ between sexes or between members and non-members of a diabetes support group. Median knowledge scores among non-farmers were significantly higher than among farmers (Mdn=5 vs. Mdn=3.5, U=1955.5, z=-2.767, p=0.001, r=-0.182). Knowledge was positively correlated with education (rho=0.238, p<0.001) and negatively correlated with age at diagnosis (rho=-0.224, p<0.001) and current age of participants (rho=-0.206, p<0.05). Age was negatively correlated with education (rho=-0.189, p<0.05).

2.3.5 Management of diabetes

Sixty-one percent of patients were taking oral anti-diabetic drugs (OADs), 33% were on insulin, 3% were on both OAD and insulin, and 3% were not taking any glucose-lowering medication. The distribution of participants using one OAD or more, and/or insulin is shown in Table 4, p.24. Insulin usage was higher among male compared to female participants (X^2=4.195, p=0.041).

Table 4 Medical therapy of diabetic patients

Type of medication [%]	Overall (n=155)	Female (n=82)	Male (n=73)
No oral anti-diabetic drug	3.9	3.6	4.1
One oral anti-diabetic drug	20.6	25.6	15.1
Two oral anti-diabetic drugs	39.4	41.5	37.0
Three oral anti-diabetic drugs	0.6	1.2	0
Insulin	32.9	25.6	41.1
Insulin + oral anti-diabetic drug	2.6	2.4	2.7

Fifty-one percent were members of the National Health Insurance Fund (NHIF). Patients who were teachers or retired had better coverage than other occupational groups, with 91% and 71% being insured, respectively. The share of non-insured patients was greater among the business sector, artisans, housewives, and students. Among the remaining professions, approximately 50% were members of NHIF. Medication was either paid for by the insurance system, through donations (5%), or by patients if no insurance was available. Median weekly costs were 12,000 TSH and tended to be higher for insulin (15,000 TSH) compared to OAD (10,000 TSH). No information was collected on the availability of medications and medical adherence. At the time of the survey, a regular checkup and consultation with a doctor cost 1000 TSH and was covered by insurance, donation, or the patient. The plurality (47%) of the patients went for checkup twice a year (Table 5). The frequency of regular checkups at the clinics did not differ between insured and non-insured participants or females and males.

Table 5 Checkup frequency of diabetic patients

Frequency [%]	Overall (n=155)
Twice a week	0.6
Weekly	6.5
Monthly	34.2
Every two months	2.6
3-5 times per year	50.3
Twice per year	2.6
Once per year	3.2

Almost 70% felt that their diabetes was well controlled, 9% felt that their diabetes was not well controlled, and 22% did not know. Eighteen percent of the patients were members of a diabetes support group. Patients were asked whether they thought that eating and physical activity habits influenced blood glucose levels. An affirmative answer was given by 87% and 88% of patients, respectively, and 97% and 89% said they had changed their habits. The majority (75%) stated they had reduced carbohydrate and sugar intake and increased vegetable intake (52%) as well as reduced fat and fried food (14%). In regard to physical activity, patients said they included walking (62%), running (15%), more farm work (18%), and more household chores (18%) into their physical activities.

2.4 Discussion

2.4.1 Associations between diabetes with demographics and anthropometrics

This study included 155 adult patients with a median age of 57 years, comparable to age distributions in other diabetes studies conducted in Tanzania (Brown *et al.* 2014; Chiwanga *et al.* 2015; Rwegerera 2014). These results are consistent with estimations by the IDF, in which 50% of all diabetic cases fall into the age range of 40 to 59 years (IDF 2013). In the current study, farmers were significantly older than non-farmers at diagnosis, with no difference in BMI. This difference may be due to higher physical activity among farmers and, thus, delayed onset of diabetes. Physical inactivity is one factor that can influence the development of diabetes type 2 (Manson *et al.* 1991; Sigal *et al.* 2006). Information on physical activity in Sub-Saharan African countries is limited (Mbanya *et al.* 2010). The current findings suggest physical activity may be important in delaying the onset of diabetes. As rates of sedentary work increase, physical activity outside of work should be explored.

In Tanzania, the national ratio of men to women is 49% to 50% (National Bureau of Statistics, Ministry of Finance, *et al.* 2013; National Bureau of Statistics & Ministry of Finance 2013), which is similar to the ratio of 47% to 53% in the current study. According to the IDF, there is no significant difference between sexes, although more men are expected to have diabetes by 2035 (IDF 2013). In the current study, more participants were married or widowed than in the Tanzanian Demographic Health survey; this can be attributed to the higher median age in the current study than in the overall population (National Bureau of Statistics *et al.* 2011).

The median household size of 5 in the current study is similar to the median of 4.9 in the Mainland of Tanzania (National Bureau of Statistics *et al.* 2011).

Fifty-one percent of the diabetic patients were members of the National Health Insurance Fund (NHIF). This fund was established in 1999 and aims to include all formal sector employees. The Kilimanjaro Region has an enrollment rate of 8%. Benefits of NHIF include registration and consultation, and the payment of medical costs, investigations fees, and impatient care services, among others (Ministry of Health and Social Welfare 2007; National Health Insurance Fund 2013).

Overweight and obesity are among the modifiable risk factors that contribute to the development of type 2 diabetes mellitus. Several Sub-Saharan African studies have found associations between overweight and obesity and diabetes (Mbanya *et al.* 2010; Mclarty *et al.* 1989; Aspray *et al.* 2000; Amoah *et al.* 2002; Motala *et al.* 2008). In many low- and middle-income countries, people associate overweight or obesity with a healthy and affluent lifestyle, and not with impaired health and increased risk factors for diseases (Sircar *et al.* 2010; McLaren 2007). Female participants in the current study had significantly higher BMI values and higher percentage of obesity than male participants. These sex discrepancies were also seen in other Tanzanian study settings (Kavishe *et al.* 2015; Njelekela *et al.* 2009). A study in urban Tanzania found a higher risk for signs of metabolic syndrome among obese women (Njelekela *et al.* 2009). Although females tended to be younger at diagnosis, having a higher BMI than males, BMI was also positively correlated with age at diagnosis in the overall study population. A combination of increased BMI and age might be a risk factor among the current study population, regardless of sex. However, this relationship needs further investigation with a larger sample size. Although mean BMI was similar to a study conducted at KCMC in 1999 (Hoffmeister *et al.* 2005), obesity rates among women were more than double in the current study (8% vs. 17%). Unlike the 1999 study (Hoffmeister *et al.* 2005), the current study also included type I diabetic patients, which usually do not have body weight in overweight or obese ranges. Thus, rates of overweight and obesity among type 2 diabetic patients alone may have been even higher. However, as no data on the type of diabetes was collected from the medical charts, no separate calculation was performed. Data from the founding years of the diabetes clinic at KCMC showed obesity prevalence of 15% among type 2 diabetic patients (Neuhann *et*

al. 2002). A study at the Muhimbili National Hospital in Dar es Salaam showed rates of 40% and 32% overweight and obesity among type 2 diabetes patients, respectively (Rwegerera 2014). In Tanzania, overweight and obesity rates are higher among women and urban residents compared to men and rural residents (Kavishe *et al.* 2015; Njelekela *et al.* 2009), although rates are increasing in rural areas as well (Keding *et al.* 2013). In urban areas, 36% are considered overweight or obese. No data on the nutritional status of men is presented in the Tanzania Demographic Health Survey from 2010 (National Bureau of Statistics *et al.* 2011).

Body weight gain of diabetic patients can also occur due to side effects of OAD, especially of sulfonylureas (Mitri *et al.* 2009) . A study follow-up assessment has shown that patients with sulfonylureas treatment increase their body weight by 5 kg over a mean duration of 6 years after starting with the medication (UKPDS 1998). Table 6, p. 31 indicates what types of OAD are associated with body weight gain. Insulin therapy is often associated with weight gain, mainly in the first months after starting the drug regimen (Mitri *et al.* 2009; Yki-Järvinen *et al.* 2012). Approaches to manage body weight gain due to medical therapy in diabetic patients include the use of weight loss drugs such as orlistat (Berne *et al.* 2005) and others (Hollander 2007). However, weight loss or stabilization of body weight with the help of lifestyle adjustments in addition to the intake of hypoglycemic agents may be appropriate and cost-effective to reach targeted glycemic control instead of adding addition medications to control for weight gain (Mitri *et al.* 2009).

2.4.2 Low knowledge and usage of bitter gourd

Only 7% of diabetic patients knew bitter gourd. This may be due to the fact that bitter gourd is mainly collected from the wild and used in the Asian cuisine in East Africa (Njoroge *et al.* 1994). At the time of the study, bitter gourd was available from one vendor at the local center market or from private people who grew bitter gourd in their garden. By the end of 2011, bitter gourd (Figure 5, p. 28) was also available at the newly established Kenyan supermarket chain Nakumatt in Moshi (Rawlings 2011). However, the commonly reported consumption of bitter tasting vegetables among interviewees and the use of phytomedicine show that there is a positive attitude towards medicinal plants and their usage.

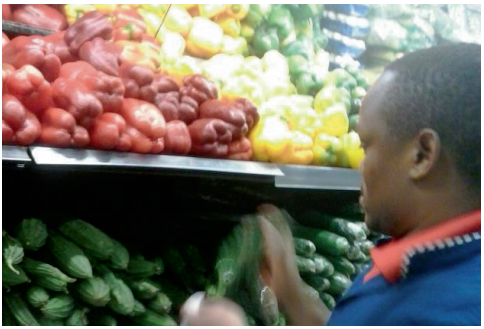


Figure 5 Bitter gourd fruits sold at the local center market in Moshi

2.4.3 Health-related and economic burden

Approximately half of the participants had first- or second-degree relatives who were diabetic. Similar and even higher rates were also found elsewhere (Guler *et al.* 2011). A study among participants with gestational diabetes reported that, in the urban area, 14% had a family history of diabetes (Mwanri *et al.* 2014). This underlines that a family history of diabetes is a risk factor for the disease. Having more than one family member suffering from diabetes may increase financial burden on the family with regard to medical care.

Only one participant reported developing diabetes during pregnancy. In a study conducted in Dar es Salaam and Kilombero District, 5.9% of pregnant participants were diagnosed with gestational diabetes with a significant difference between urban (8.4%) and rural (1.0%) settings (Mwanri *et al.* 2014). Longitudinal studies are needed to assess the extent of the progression of gestational diabetes to type 2 diabetes mellitus.

The median duration of 8 years since diagnosis of diabetes was comparable to findings in other studies (Sircar *et al.* 2010; Al-Qazaz *et al.* 2011; Sweileh *et al.* 2014). The complication most mentioned by patients in the current study was related to retinopathy with impaired sight

and blindness. Retinopathy is one of the most common microvascular complications among diabetic patients (Fowler 2008) and might by related to the severity of hyperglycemia and the presence of hypertension (Group UKPDS 1998). Almost half of the patients reported having hypertension. Hypertension is a common comorbidity among diabetic patients, with rates ranging from 20 to 60%, and may require additional medical therapy to prevent complications (ADA 2003).

A study conducted in Dar es Salaam found a 15.3% prevalence of diabetic foot ulcers (Chiwanga *et al.* 2015). Foot ulcers are a major risk factor for future amputations (Boulton *et al.* 2005). In the current study, amputations were reported by 1.3% of patients. Although the current study was not representative, more diabetic patients of KCMC and MLH may have had amputations. In a resource-poor setting like the current study, patients with amputations may face greater difficulties in traveling to diabetes clinics. To avoid a progression of foot ulcers to amputations, regular foot care can include examinations by a doctor and self care by patients. In the study in Dar es Salaam, only 27.5% of patients said they had a foot examination by a doctor since diagnosis, and many patients did not perform foot self care (Chiwanga *et al.* 2015).

In the current study, the long delay between patients' initial perceptions of symptoms and diagnoses may have been due to an unfamiliarity with the symptoms of diabetes. A qualitative study showed that symptoms of diabetes mellitus, e.g., frequent urination and itching around the genital area, have been mistaken by health professionals for signs of urinary tract infections and sexually transmitted diseases. Further, it was reported that diabetes symptoms were mistaken for signs of malaria and HIV. In the case of HIV, patients were reluctant to seek medical care for fear of stigmatization. The study concluded that knowledge about diabetes was scarce among the public and among health professionals, and that patients acquired knowledge after diagnosis (Metta *et al.* 2015). This may be the case for the current setting as well, where posters on diabetes symptoms, complications, and foot care were displayed in the examination rooms and consultation office. Lack of awareness of diabetic glucose levels has been reported for Tanzania (Kavishe *et al.* 2015).

Approximately 17% of the participants reported having given up something to pay for diabetes management. Most of them were not members of NHIF. The financial burden and occasional dependence of diabetic patients on other family members as caregivers or financial

supporters, were mentioned by diabetic patients in a similar setting (Kolling *et al.* 2010). Checkup prices reduced from an initial cost of 8,000 TSH in the founding years of the diabetes clinic at KCMC (Neuhann *et al.* 2002) to 1,000 TSH.

2.4.4 Knowledge on diabetes – achievements and challenges

In the current study, 75% of participants did not know what type of diabetes they had. However, according to the ADA, it is more important to understand the pathogenesis of hyperglycemia and effective treatment (ADA 2010). Among patients, symptoms were more commonly known than causes or complications. However, this knowledge was probably gained after diagnosis. This assumption is similar to findings by Metta et al. who conclude that awareness and knowledge about diabetes signs and symptoms was limited, especially prior to diagnosis (Metta *et al.* 2015). Knowledge was positively correlated with education and being a non-farmer. Educational level was significantly higher among non-farmers than farmers. Other studies also found an association between education and knowledge (Chiwanga *et al.* 2015; Guler *et al.* 2011) as well as between education and the likeliness of medical adherence (Sweileh *et al.* 2014), whereas others did not detect a relationship between education and knowledge on and practices in diabetes (Sircar *et al.* 2010). As education was negatively correlated with age, knowledge was also negatively correlated with current age and age at diagnosis. This was also seen elsewhere (Guler *et al.* 2011).

2.4.5 Problems in the management of diabetes

Almost all patients in the current study were taking some form of medication for blood glucose control, either OAD, insulin, or both. Patients using only OAD take a combination of metformin and sulfonylurea tablets (38%), only sulfonylurea tablets (14%), or only metformin tablets (9%). Patients were not asked about knowledge of the different kinds of medications used and their modes of action. An understanding of hyperglycemia and its treatment possibilities is important for a successful treatment (ADA 2010), so future studies should assess patient knowledge of medications used and the underlying pathogenesis of hyperglycemia that is treated. Table 6, p. 31, shows an overview and hypoglycemic medications.

Table 6 Overview on oral anti-diabetic drugs (Biesalksi, HK *et al.* 2010)

Active ingredient	Can cause hypoglycemia (in monotherapy)	Increases insulin secretion	Weight gain
Sulfonylureas			
Glibenclamide	yes	yes	yes
Gliclazide	yes	yes	yes
Glimepirid	yes	yes	yes
Gliquidon	yes	yes	yes
Glinides			
Repaglinide	yes	yes	yes
Nateglinide	yes	yes	yes
Biguanides			
Metformin	no	no	no
Dipeptidyl Peptidase-IV Inhibitors			
Sitagliptin	no	yes	no
Vildagliptin	no	yes	no
Saxagliptin	no	yes	no
Thiazolidinedione			
Pioglitazone	no	no	yes
Rosiglitazone	no	no	
α-glucosidase Inhibitors			
Acarbose	no	no	no
Miglitol	no	no	no

The intake of more than one OAD was also reported in other studies (Chiwanga *et al.* 2015). The current study did not assess medical adherence or availability of medical care. A recent review identified several factors that influence medical adherence in patients who take multiple medications. These include social and economic factors, medication-therapy-related factors, patient-related factors, and health-care-provider and health-system-related factors (Marzec *et al.* 2013). During conversations with current study participants, they mentioned difficulties in obtaining a constant medical supply, especially in the case of insulin. A similar observation was made in a study among urban poor diabetics in Dar es Salaam. There, a patient described attempts to obtain insulin as very challenging and expensive. In case of the unavailability of OAD, patients may seek treatment from traditional healers (Kolling *et al.* 2010). A comparison

(Robertson *et al.* 2015) of three different assessments (Peck *et al.* 2014b; Ministry of Health and Social Welfare, Tanzania 2013; WHO/HAI 2008) of medicine availability in Tanzania revealed a shortage of medications for diabetes and hypertension in both governmental and private facilities. Availability of metformin and glibenclamide ranged from 33-57% and 19-59%, respectively. Availability of medicine was influenced by the managing authority, facility level, and setting. The authors concluded that availability was higher in mission-owned and privately owned institutions than in government facilities, was higher in hospitals than in health centers and dispensaries, and higher in urban than in rural settings. Reasons for suboptimal availability were not explored. Another study reported that medicines for diabetic patients in Dar es Salaam are available in private pharmacies (84%) and hospital pharmacies (16%) (Brown *et al.* 2014).

Approximately 50% of current patients had to pay for their medication and glucose control, which can also influence medical adherence. A study among patients at Muhimbili National Hospital in Dar es Salaam reported adherence rates of 60% and 71% during the previous week and three months, respectively. Adherence was associated with concurrent use of other medications and was found to be good among elderly patients. Poor adherence was linked to costs and side effects (Rwegerera 2014). Another study among diabetic patients in Palestine revealed an even lower adherence of 57%. Knowledge about diabetes was associated with adherence. Patients with higher diabetes knowledge scores were less likely to be nonadherent. Seventeen percent stopped taking their medication after they felt their diabetes symptoms were controlled (Sweileh *et al.* 2014). Medical adherence is important for glycemic control. A study in Malaysia revealed that monotherapy, higher diabetes knowledge, and higher medical adherence were associated with glycemic control (Al-Qazaz *et al.* 2011).

The current study did not assess medical data on glycemic control. Regular measurements of HbA_{1c} were reported to be lacking among participants. A study conducted at KCMC in 2006 showed that 65% of diabetic patients (type 1 and type 2) had HbA_{1c} levels >8.5% (Michaelsen, Jens Kersten 2011). The availability of measurements of long-term glucose parameters should be evaluated to improve glucose control among patients. In contrast to high-income countries, Tanzania has few diabetic patients who own a glucometer for self monitoring of glucose levels (Smide *et al.* 2002). The presence of only three clinical staff members poses a major challenge to providing adequate care to diabetic patients. Such a lack of human resources

was also demonstrated in other Tanzanian settings (Peck *et al.* 2014b). Availability of equipment for diabetes diagnosis and management needs to be improved, despite efforts to do so during the past decade.

Most of the patients stated to have changed their dietary intake patterns and physical activity patterns after the diagnosis. Most reported changes were increased intake of vegetables and an increase in physical activity. In regard to physical activity, diabetic patients should engage in at least 150 min per week of moderate aerobic physical activity on at least three days per week with no more than two days without physical activity (ADA 2016). Recommendations for medical nutrition therapy among type 2 diabetic patients with no renal impairment include intake of carbohydrates from whole grains, fruits, and vegetables, protein (15-20% of overall energy intake), saturated fat <10% of total energy intake, one alcoholic beverage for women and two for men, among other (Franz *et al.* 2002). More detailed recommendations are given in the appendix (D).

2.4.6 Limitations

The current study had several limitations. Due to the small sample size, results cannot be generalized. Patients were recruited by convenience sampling and interviewed on the first upper level of a building, which may have prevented participation of patients with advanced complications such as amputation and blindness. No data were collected with regard to glycemic control, medical adherence, or treatment availability. However, the current study collected data to explore existing problems among diabetic patients in the Kilimanjaro Region. The findings of the study were similar to those of other studies. Thus, ideas for future intervention programs and research questions could be derived.

2.4.7 Conclusion and outlook

The current survey showed that diabetes knowledge was present among patients, although it was presumably acquired after diagnosis. In addition, diabetes care imposed extra burdens on some participants. The existence of complications shows the need to improve diabetes management, including possibilities to monitor long-term glucose levels. Overall, there is a need to further educate patients about diabetic complications and further expand research on lifestyle changes after diagnosis.

Suggested interventions for the Kilimanjaro Region

- Education about diabetes signs and symptoms and risk factors at public and private places, such as workplaces, churches, mosques, schools, supermarkets, and news media
- Increase in health staff for diabetes care
- Establishment of equipment for long-term glucose control
- Establishment of equipment for detection of diabetes-related complications
- Establishment of local diabetes support groups
- Education about lifestyle changes among diabetic patients
- Systematic monitoring of medicine availability at health facilities
- Exploration of possibilities to increase access to medical insurance

Suggested follow-up research topics

- Medical adherence and possible barriers
- Medical adherence and glycemic outcomes during religious fasting
- Food intake and physical activity among diabetic patients
- Use of traditional medicine among diabetic patients
- Knowledge about diabetes among communities
- Potential means to spread and increase knowledge about diabetes

Chapter 3: Anti-diabetic effects of bitter gourd consumption for two months among pre-diabetics in Moshi, Tanzania

3.1 Objectives

The major objective of the recruitment procedure was to recruit subjects for the dietary intervention study in Moshi, Tanzania. Further, this dissertation aimed to elucidate the process and approach of the recruitment procedure, health aspects of the participants, and enrollment rate.

The major objective of the intervention study was to assess anti-diabetic effects of daily bitter gourd consumption of 2.5 g powder over the course of eight weeks among pre-diabetic persons. The primary endpoint was FPG measured at endline with an expected difference in between bitter gourd and placebo group. Secondary endpoints were HbA_{1c}, insulin, high-density lipoprotein (HDL), cholesterol (Chol), triglycerides (TG), BP, and BMI.

3.2 Method section

3.2.1 Study area and subjects

The study was conducted at the Kilimanjaro Clinical Research Institute (KCRI) located in Moshi Municipality (Figure 6, p. 36) in the Kilimanjaro Region, Tanzania. The Kilimanjaro Region is located in northern Tanzania and had a population of 1,640,087 in 2012 (National Bureau of Statistics & Ministry of Finance 2013). Participants were recruited during a two-stage screening procedure.

The inclusion criteria for eligible participants were: pre-diabetes diagnosis based on the ADA's FPG cut-off values of 5.6-6.9 mmol/L (100-125 mg/dL) (with IFG on two days or IFG on one day in addition to eligible HbA_{1c}), HbA_{1c} of 5.7-7.5% (39-58% mmol/mol), BMI of 27-35 kg/m², BP of 90/60-160/110 mmHg, age between 30-65 years, and waist circumference (WC) >80 cm for women and >90 cm for men. Exclusion criteria were: having any clinically diagnosed disease, taking medication regularly, having an identified glucose-6-phosphatase-dehydrogenase (G6PD) deficiency, heavy alcohol consumption, pregnancy, and breastfeeding. The study-related HbA_{1c} upper limit exceeded ADA recommended cut-off points for pre-diabetes. During the screening process, HbA_{1c} levels were found to be high, whereas the FPG

levels of the same participants were moderate. The use of a higher cut-off in the HbA_{1c} criterion was approved by the Institutional Review Boards of National Institute for Medical Research (NIMR) and Kilimanjaro Christian Medical College. During 2013/2014, HbA_{1c} cartridges were recalibrated by HemoCue®, which resulted in lower readings compared to old cartridges. However, a correction factor was not provided by the manufacturer, and was instead calculated by comparing old and new cartridges analyzed by the HemoCue® 501 analyzer (HemoCue®GmbH, Germany) and another HbA_{1c} point-of-care analyzer (DCA Vantage Analyzer, Siemens, Germany). Corrected HbA_{1c} levels are presented in the current analysis. During the screening process, eligibility criteria were based on uncorrected HbA_{1c} values.

Figure 6 Location of the study area in Tanzania (Destination360 2006)

3.2.2 Study design and randomization

The current study was a randomized, single-blind, placebo-controlled, cross-over designed intervention study (Figure 7, p. 38). This superiority study was divided into an AB-BA sequence. "Group 1" (AB) started with bitter gourd supplementation, followed by placebo. A washout period of four weeks was conducted between the two supplementation periods. "Group 2" (BA) started with placebo followed by bitter gourd supplementation with a four-week washout period in between. A four-week washout period has been shown previously to prevent carry-over effects (Tsai *et al.* 2012).

After completion of the screening, all identification codes of eligible participants were entered into SPSS. As the screening did not result in a number of participants exceeding the calculated sample size, all eligible participants were included into the randomization process and placed into sequence groups. Randomization was performed using the Mersenne Twister random number generator (Matsumoto *et al.* 1998). To ensure equal distributions of female and male participants, both sexes were separately randomized to each group.

Participants were blinded to the group assignment, provided with sachets containing either bitter gourd powder or placebo (cucumber), and instructed to mix the powder with 150 mL of provided drinking water and consume it after a main meal (appendix J). Because almost no previous studies were conducted on bitter gourd use by pre-diabetics, the research coordinators were not blinded to the group assignment, so they could intervene in case of any hypoglycemic event caused by bitter gourd supplementation. All participants were instructed not to change their eating habits or physical activities during the intervention study. Compliance with instructions was assessed in weekly regular checkup questionnaires. In addition, participants received a calendar and stickers to mark their consumption of sachet contents and presented the calendar at each visit.

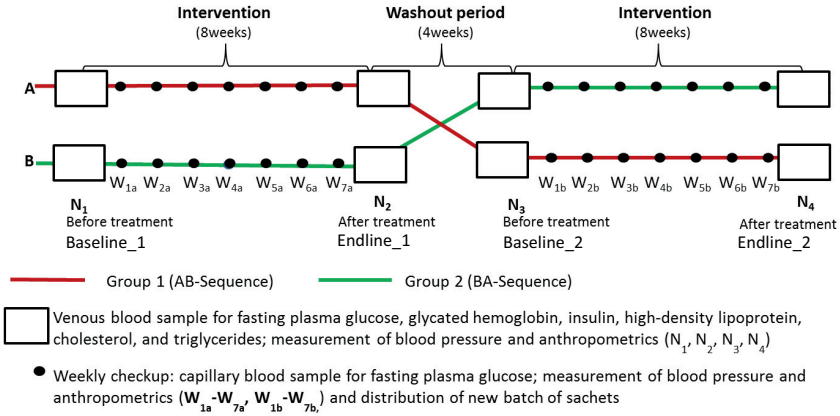


Figure 7 Design and assessment time points of the intervention study

3.2.3 Sample size

Sample size was calculated using G*Power 3.1 (Faul *et al.* 2007). The calculation was based on an expected difference of 0.56 mmol/L (10 mg/dL) in mean FPG between groups, a standard deviation of 0.94 mmol/L (17mg/dL) in each group, an alpha level of 0.05 and a power of 0.95 and was equal to 63 participants. However, this was based on a paired t-test. A period effect was observed after the completion of the study, making the comparison of matched pairs inappropriate. Thus, the sample size was recalculated based on a two-sample t-test, with a standard deviation of 0.56 mmol/l (10mg/dl) in each group, and with the same expected difference, alpha level, and power. The recalculated sample size was 54 participants.

3.2.4 Preparation of sachets and dosage

The bitter gourd variety used in the study was NS1020 from Namdhari Seeds Pvt. Ltd® (India) and was grown and harvested at the AVRDC in Taiwan between July and September 2012. The cucumber variety used was MALANI™ from Seminis® (India), also grown at AVRDC. Bitter gourd and cucumber fruits were washed with clean water and dipped into water containing 1-2% hydrogen peroxide. Fruits, including seeds and skin, were chopped, freeze-dried, and ground

into powder (80 mesh). Processing was performed by Challenge Bioproducts Co., Ltd. (Taiwan). Mixing of powders with additives and packing was performed by TAI WON FOOD INDUSTRIAL CO., Lt TDTaiwan). Both were certified according to ISO 22000 and HACCP. The daily dosage of bitter gourd was 2.5 g, based on results of a previous animal trial in which the equivalent dosage of 500 mg/kg body weight improved insulin sensitivity in high-fat-diet mice. In the same trial, raw bitter gourd was more effective than cooked bitter gourd (unpublished data). A daily dosage up to 4.8 g has been found to be safe for humans (Tsai *et al.* 2012). To mask the bitter taste, 0.75 g alpha-cyclodextrin mixed with 2% lemon peel oil (CAS Number 8008-56-8), 75 mg beta-cyclodextrin, 15 mg steviol glyscoside, and 0.75 g cucumber powder were added to the bitter gourd powder. The placebo contained 3.25 g of raw cucumber powder in addition to the aforementioned ingredients (except additional cucumber powder). Alpha-cyclodextrin was purchased from SEI CHENG CHEMICAL CO., LTD. Company (Taiwan), beta-cyclodextrin was purchased from Baolingbao Biology Co., Ltd (China), and steviol glycoside was purchased from YIH YUAN FOOD ADDITIVES & CHEMICAL INDUSTRIAL CO., LTD. (Taiwan). All concentrations were in accordance with regulations of the Food and Drug Administration (Nutrition Center for Food Safety and Applied 2004; Nutrition Center for Food Safety and Applied 2001) and of the European Union (European Commission 2011). Sachets were shipped to Tanzania after obtaining permission from the Tanzanian Food and Drug Authority (TFDA) and stored in a cooling room until distribution. Participants received sachets and drinking water on a weekly basis during their regular checkup appointments. A closable cup, with a marking at 150 ml, was provided to mix the powder and water.

3.2.5 Recruitment procedure – two-stage screening approach

The recruitment procedure for pre-diabetic participants was conducted in Moshi Urban District, one of the six districts of the Kilimanjaro Region in northern Tanzania. The Kilimanjaro Region had a population of 1,640,087 in 2012 (National Bureau of Statistics & Ministry of Finance 2013). Moshi Municipality, the capital of Moshi Urban District, is divided into 21 wards (Moshi Municipality Council 2012) of which seven (Longuo, Rau, Karanga, Mawenzi, Majengo, Mji Mpya, Njoro, Pasua) were chosen as pre-screening areas (Figure 8, p. 40). They were chosen due to their proximity to the screening facility in Longuo or due to their use in previous studies

(Ludwig *et al.* 2013). Screening took place at the KCRI, which is the third pillar of the Good Samaritan Foundation and is closely associated with the KCMC (Manta Ray Media 2015).

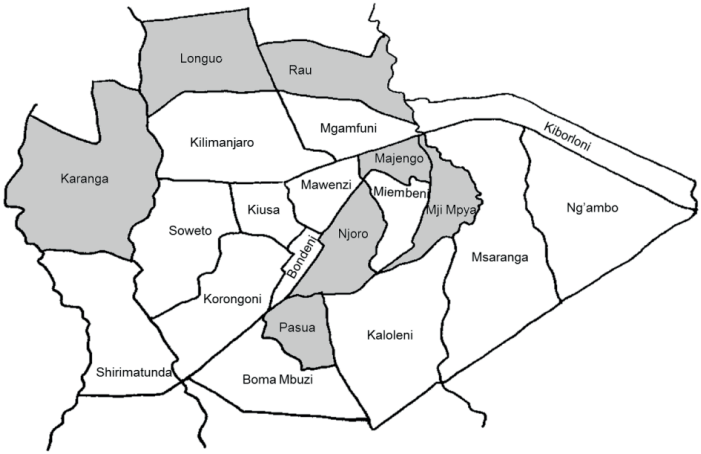


Figure 8 Selected wards (highlighted in grey) for the recruitment procedure in Moshi adapted from (Moshi Municipality Council 2012)

The recruitment procedure was divided into two phases. Between April and October 2013, a pre-screening phase informed institutions and congregations of the upcoming research study. When possible, people were screened for eligible BMI and age during this phase. The pre-screening took place at 16 different settings in Moshi and included the following gatherings or institutions: single people from Njoro and Pasua identified as pre-diabetics in a previous study, clinical conference for doctors and nurses at KCMC, radio announcement, three Lutheran churches, four Catholic churches, one convent, two banks, teachers at two primary schools, staff and lecturers at one university, one mosque, one police academy, one revenue authority, and KCRI. Before any data was collected, information was provided about the rationale, aims, procedures, and target group. After the information session, people had the opportunity to ask questions and to stay for a subsequent data assessment. The type of data assessment differed between pre-screening sites in regard to contact information, age, BMI, and BP. The latter was not yet matched to inclusion criteria. In the early stages of the pre-screening, body weight was

measured with an analogue scale and height with an elastic measurement tape fixed to a straight wall. In the later stages, body weight was measured with a digital scale (Seca 877 Germany) and portable stadiometer (Seca 217, Germany). Body mass index was calculated as bodyweight in kg divided by the square of body height in m. While seated, each participant's BP was measured on the left arm using a Visomat Double Comfort BP cuff (range: systolic 50-250 mmHg, diastolic 40-150 mmHg, Uebe Medical GmbH, Germany). All measurements were performed once. Body mass index and BP values were categorized according to WHO guidelines (WHO 1999, WHO 2015) and American Heart Association (AHA 2015) guidelines, respectively. All participants with eligible BMI and age were invited to the screening for pre-diabetes. Every eligible participant was called and instructed to fast overnight prior to a scheduled appointment.

The screening for pre-diabetes and all other eligibility criteria took place at the KCRI between July and October 2013. Pre-screening and screening activities at KCRI were performed simultaneously. Screening appointments were scheduled between 7:30 and 10:30 a.m. An assessment of body weight and height, a questionnaire-based interview, and a BP measurement were performed in assessment room one. Fasting plasma glucose and HbA_{1c} were measured in assessment room two. The screening time was about five minutes in each room. Body weight was measured using a digital scale (Seca 877, Germany). Body height was measured using a portable stadiometer (Seca 217, Germany) according to FANTA protocol (Cogill 2003), with participants dressed in light clothing and without shoes. Measurements were performed only once. Waist circumference and hip circumference (data not shown) were measured twice using a retractable measurement band according to STEPS Surveillance (WHO STEPS Surveillance 2008). If the difference between the two measurements was greater than 1 cm, a third measurement was performed. The mean of the measurements was then recorded. Afterward, the participant was asked to sit for an interview. A standardized screening questionnaire was used to assess socioeconomic and health-related data (appendix E, F). After five minutes, BP was measured once with the participant seated.

In assessment room two, capillary blood samples were obtained from a dry, disinfected fingertip using one-way lancets. Fasting plasma glucose was measured using Accuchek Aviva® (Roche Diagnostics, Switzerland). Glycosylated hemoglobin was measured with HemoCue® 501

analyzer, (HemoCue® GmbH, Germany). Both appliances are point-of-care devices and results were available after a few seconds for FPG and after five minutes for HbA_{1c}. Participants with unknown diabetic glucose levels or diabetics with high glucose levels were advised to go to their nearest clinic for further medical consultation. During a run-in period, G6PD deficiency was assessed using CareStart™ G6PD (Access Bio, USA), a rapid test kit for capillary blood. All participants were reimbursed for their traveling and given a chart of their data, reference ranges, and a small snack. If requested, participants were given counseling for nutrition and physical activity as part of a healthy lifestyle.

3.2.6 Data collection

All data were collected and documented into patients' files during the intervention study and into case report forms. Further, each participant received his or her measure values on a separate form.

Demographics, anthropometrics and blood pressure

Socioeconomic, demographic, and medical data were obtained using a standardized questionnaire at the baseline assessment before the start of the intervention study. Data were obtained about marital status, educational status, profession, and medical history. Questionnaires were compiled in English and then forward and backward translated to check for inconsistencies. Interviews were conducted in Swahili, the local national language.

Anthropometric measurements were conducted with the same devices as used during the screening. Body weight was measured to the nearest 0.1 kg using a digital scale (Seca 877, Germany). Body height was measured to the nearest 0.5 cm using a portable stadiometer (Seca 217, Germany). Measurements were performed once. Body mass index was calculated as stated before weight. Waist circumference and hip circumference (data not shown) were measured twice using a retractable measurement band. If the difference between the two measurements was greater than 1 cm, a third measurement was performed. The mean of the measurements was then recorded.

After a five minute rest period in a seated position, each participant's BP was measured using a digital blood pressure monitor on the left arm (Visomat Double Comfort, Uebe Medical

GmbH, Germany). Body weight and BP were assessed before and after each supplementation phase and at every weekly visit of the participants.

Blood samples

Before and after each supplementation period, a 5 ml venous blood sample was drawn from participants by a certified nurse. Participants were instructed to arrive after at least eight hours of fasting and were rescheduled if they had not fasted. From the venous blood samples, concentrations of FPG, HDL, TG, Chol, insulin, glutamate pyruvate transaminase (GPT), and creatinine were analyzed. The latter two were assessed as parameters for liver and kidney function. Fasting plasma glucose, HDL, TG, Chol, GPT, and creatinine were analyzed using ReflotronPlus®, Roche Germany. Reagents were purchased by Roche Germany. Insulin was analyzed via the ELISA technique using a BioTek® Human Insulin (INS) ELISA Kit manufactured by Bioassay Technology Laboratory, Shanghai, China.

Capillary blood samples were obtained from a dry, disinfected fingertip to assess capillary FPG and HbA_{1c}. Fasting plasma glucose was assessed using Accu-Chek Aviva® (Roche Diagnostics, Switzerland). Glycosylated hemoglobin was measured using HemoCue® 501 analyzer (HemoCue® GmbH, Germany). Results were ready after a few seconds for FPG and after five minutes for HbA_{1c}. Capillary blood samples were obtained before and after each supplementation period, and also during weekly visits of participants. The weekly measurements are not shown here. After each assessment appointment, participants were provided with a small snack.

Food intake and physical activity

To assess changes in food intake and physical activity, a qualitative food frequency questionnaire (FFQ) (appendix H) and physical activity questionnaire (PAQ) (appendix I) were conducted. Participants were interviewed during the run-in period (one week before the start of the intervention) and at the end of the intervention. The FFQ covered the previous month. To compare food intake data, a monthly food variety score was calculated. In regard to changes in physical activity, only the sports section of the PAQ was compared. Both questionnaires were pre-tested in a study in 2012 in the same study area and adjusted afterward to cover locally available and consumed foods. Additionally, the weekly regular checkup questionnaire included

questions on whether the participant changed his or her food intake and physical activity during the previous week and, if yes, what kinds of changes were made.

Adverse events and side effects

Adverse events and side effects reported by participants were recorded on the regular checkup questionnaire (appendix G) during each weekly visit. This questionnaire also included the use of medication during the previous week. In addition, GPT and creatinine values were checked after every assessment for clinically elevated values.

3.3 Statistical analyses

Statistical analyses of the recruitment procedure

Data entry and analysis were performed using Microsoft Excel 2013, SPSS version 22 (SPSS Inc, Chicago Illinois), and Stata version 14. Variables are expressed as frequencies or as median and interquartile range. Only WC was consistent with a normal distribution and described by a mean and standard deviation. A Mann-Whitney U-test was used to identify differences in continuous variables between male and female participants. A Chi-squared test was used to identify differences between categories in categorical variables. Among the pre-screening sample, Spearman's rho was calculated to assess correlations. Concordance between FPG and HbA_{1c} measurements of dysglycemia was calculated using Krippendorff's alpha (Hayes *et al.* 2007). Dysglycemia was defined by FPG ≥5.6 mmol/L (≥100 mg/dL) or HbA_{1c} ≥5.7% (≥39 mmol/mol). Concordance of the glycemic status (normal, pre-diabetic, or diabetic) will be presented using cross tabulation. Among the screening sample, a non-linear model with seemingly unrelated regression (SUR) (Wooldridge 2010) was computed to analyze effects of age on FPG, HbA_{1c}, and BP, as well as to analyze effects of WC and BMI on the dependent variables. Age was controlled for gender; WC and BMI were controlled for age and gender. If necessary, the quadric variation of the centered independent variable was used. Fasting plasma glucose, HbA_{1c}, and BP were log transformed prior to analyses. For these particular models, participants who take medication regularly or were pregnant were excluded. Results were considered statistically significant for $p<0.05$.

Statistical analyses of intervention study

Double data entry and checking were performed using SPSS version 21 (SPSS Inc, Chicago Illinois). Data were analyzed using SPSS version 22 (SPSS Inc, Chicago Illinois) and Microsoft Excel 2013. Descriptive data are reported as mean and SD. Per protocol, analysis was performed for data from venous blood samples, anthropometrics, and BP. Other variables, such as socioeconomic data, were analyzed for all 52 participants who finished the study in March 2014 but had missing blood-sample data. As no capillary FPG levels were hypoglycemic and no participant showed signs of hypoglycemia, venous FPG values <3.3 mmol/L were excluded. For other variables, one extreme outlier (box plot) was excluded from the analysis of TG values. Exclusion of this outlier did not influence the statistical significance of the findings.

The difference in the primary outcome (measured FPG) between bitter gourd and placebo groups was analyzed with a CROS analysis and general linear mixed model. The CROS analysis (Freeman 1989; Senn 2002) is based on the Hills-Armitage approach (Hills *et al.* 1979), which compares calculated mean period and cross-over differences and can detect a treatment effect despite the existence of a period effect.

Second, a mixed model for fixed effect (Type III) was applied to examine treatment, period, and carry-over effects (Allison 2009). The fixed effects in this model were treatment (bitter gourd or placebo), period (period one or period two), and carry-over effects. The general linear model detected a period effect and a significant influence of the baseline FPG on the endline FPG (Table 7, p. 46). Thus, the change from baseline to endline was analyzed for differences instead of only for endline values.

Differences between baseline_1 and baseline_2 levels between Group 1 and Group 2 were checked. A two-sample t-test or Mann-Whitney test was performed if data were consistent or inconsistent with the normal distribution, respectively.

Table 7 Type III Tests of Fixed Effects with FPG at endline (N_2 + N_4) as dependent variable

Source	Numerator df	Denominator df	F	*p*
Intercept	1	83	26.629	0.000
Treatment	1	83	5.168	0.026
Carry-over	1	83	2.105	0.151
Period	1	83	1.354	0.248
FPG, baseline, (N_1 + N_3)	1	83	15.721	0.000

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	*p*	95% Confidence	
						Lower bound	Upper bound
Intercept	2.90982	0.563883	83	5.160	0.000	1.7883	4.0314
Treatment	0.221769	0.097550	83	2.273	0.026	0.0277	0.4158
Carry-over	-0.141737	0.097697	83	-1.451	0.151	-0.3361	0.0526
Period	0.116536	0.100137	83	1.164	0.248	-0.0826	0.3157
FPG, baseline, (N_1 + N_3)	0.380388	0.095936	83	3.965	0.000	0.1896	0.5712

FPG: fasting plasma glucose

3.4 Ethical considerations

The study protocol was approved by the Institutional Review Boards of NIMR (appendix K), TFDA, the Kilimanjaro Christian Medical College, the Regional Medical Office in Moshi, and the Faculty of Medicine at Giessen University, Germany. All directly involved study personnel acquired a certificate on good clinical practice prior to the start of the intervention study.

All pre-screened and screened participants gave verbal consent to participate in the recruitment procedure. Participants included in the intervention study gave written informed consent. All were informed of their right to withdraw at any time without consequences. A data transfer agreement was obtained to allow the data to be analyzed outside of Tanzania. The study is registered under the number DRKS00005131 in the German Clinical Trial Register.

4. Results

The presentation of the results is divided into two major sections. The first section presents findings of the recruitment procedure in regard to health aspects and successfully enrolled participants. The second section presents findings of the intervention study in regard to changes of the examined outcome parameters such as FPG, HbA_{1c}, and BP.

4.1 Recruitment process

4.1.1 Health profiles of pre-screened and screened participants

A total of 1,256 people were pre-screened. Of these, 888 were pre-screened outside of KCRI. The remaining 368 people were screened at KCRI, and most were friends or relatives (n=328) of invited pre-screened people or were contacted previously through public announcements (n=40). Most people attended pre-screening activities after church services. The highest rates of eligible BMI and age occurred among office workers and teachers (Table 8, p. 48)

Table 8 Pre-screening sites outside of and inside KCRI and subsequent screening attendance rates. Pre-screening at KCRI took place during regular screening hours

Pre-screening site	Pre-screened	Eligible BMI and age criteria		Attended screening	
	n	n	[%]	n	[%]
Bank	35	21	60.0	1	4.7
Churches	595	227	38.2	131	57.7
Convent	13	6	46.2	4	66.7
Mosque	40	12	30.0	7	58.3
Primary schools	62	31	50.0	22	71.0
Police academy	90	42	46.7	17	40.5
Revenue authority	38	29	76.3	19	65.5
University	15	10	66.7	10	100
Total outside KCRI	**888**	**378**	**42.5**	**211**	**55.8**
Total inside KCRI	368	171	46.6	171	100
Overall total	**1256**	**549**	**43.7**	**382**	**69.6**

Median BMI was 27.5 kg/m² (24.1; 31.3), median age was 47.0 years (37.0; 55.0), median systolic BP was 125.0 mmHg (114.0; 142.0), and median diastolic BP was 83.0 mmHg (76.0; 91.0). About 30% of participants had hypertensive BP values (Figure 9). People with high BP values were directed to go to their nearest health facility for further medical consultation.

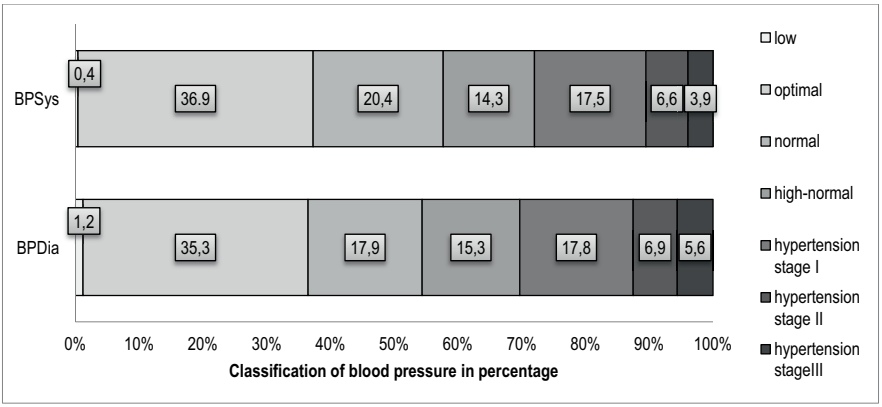


Figure 9 Classification of systolic (n=1218) and diastolic (n=1217) blood pressure (pre-screening)

As shown in Table 9, p. 50, median BMI increased across age groups until the age of 60 years. The majority of the pre-screened participants were overweight or obese (Figure 10), likely because the research team stated that it was seeking participants with an increased body weight. Systolic BP increased across age groups, reaching the highest median in the oldest age group. Diastolic BP increased up to the age group of 50-59 years. Age was correlated with systolic BP (rho=0.371) and diastolic BP (rho=0.207). Body mass index correlated with systolic BP (rho=0.144) and diastolic BP (rho=0.244). Systolic BP was highly correlated with diastolic BP (rho=0.724). All correlations were significant at the level of $p<0.001$. Systolic and diastolic BP was significantly higher in obese participants than in normal-weight participants (U=52793, z=4.833, $p<0.001$, r=0.178; U=45781, z=7.296, $p<0.001$ r=0.270, respectively).

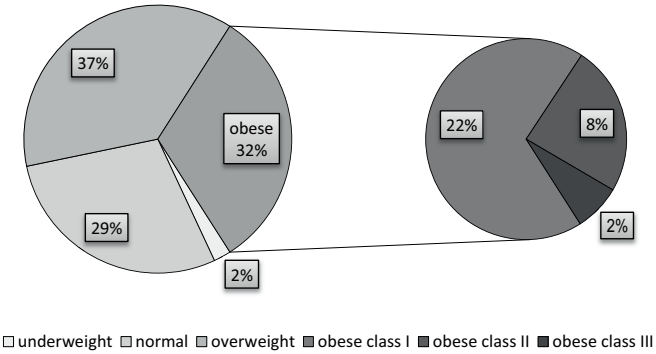


Figure 10 Classification of body mass index of the pre-screening sample, n=1252

Table 9 Body mass index and blood pressure according to age group of the pre-screening sample n=1140

Variable	15 -19	20-29	30-39	40-49	50-59	60-69	70-79	≥80
	n=9	n=96	n=237	n=316	n=322	n=124	n=26	n=10
Body mass index [kg/m²]	20.8	24.9	27.8	29.3	28.6	27.3	24.9	23.8
	21.2; 27.7	20.9; 27.7	20.9; 27.7	25.7; 32.5	25.7; 31.8	22.8; 30.5	21.6; 28.9	21.2; 31.0
Systolic blood pressure	106.0	116.0	120.2	124.0	134.0	137.0	143.5	154.0
[mmHg]	96.5;	107.5;	109.0;	114.0;	120.0;	120.0;	123.3;	141.0;
	121.0	125.8	129.0	137.0	149.0	152.0	163.0	162.5
Diastolic blood pressure	70.0	77.5	81.0	87.0	84.0	84.0	84.0	70.0
[mmHg]	64.0; 74.5	71.0; 82.8	74.0; 89.9	78.0; 92.0	79.9; 95.0	76.0; 93.0	78.0; 94.0	68.0; 95.5

A total of 382 people had an eligible age and BMI and were further screened for the remaining inclusion criteria. Fasting plasma glucose and HbA_{1c} were assessed in an additional 199 people who came to the KCRI pre-screening facility, but who did not meet age and BMI eligibility. Thus, FPG and HbA_{1c} values were available for 581 people. Based on ADA (or WHO) criteria, 55% (75%) had normal, 32% (12%) had pre-diabetic, and 13% (13%) had diabetic FPG values. Fifty-five percent of the participants with diabetic FPG values were unaware of their high glucose levels. These results were also detected in the regular screening sample of 382 participants (Table 10, p. 52). Here, 51% (73%) had normal, 35% (13%) had pre-diabetic, and 15% (15%) had diabetic FPG levels. Among the latter group, 60% were unaware of their high glucose levels. Among diagnosed diabetics (n=26), 50% were prescribed medication. However, their median FPG and HbA_{1c} values were higher compared to cases in which diabetes status was unknown (Table 12, p. 54).

According to ADA criteria for HbA_{1c}, 42% had normal, 42% had pre-diabetic, and 16% had diabetic HbA_{1c} levels. In the following, only the corrected HbA_{1c} will be presented. Concordance of dysglycemia between FPG and HbA_{1c} measures was 68%, with a Krippendorff's alpha of 0.351, which indicates low reliability. Rates of dysglycemia were higher using HbA_{1c} than FPG values. In regard to concordance of HbA_{1c} and FPG in glycemic status, 62% were in the same criteria (31% had both values normal, 20% had both values pre-diabetic, and 11% had both values diabetic). Nineteen percent had pre-diabetic HbA_{1c}, but normal FPG, and 12% had pre-diabetic FPG, but normal HbA_{1c}. The remaining 7% had other combinations. The highest concordance was observed in the diabetic category.

Forty-one percent had hypertension, defined by a systolic or diastolic BP meeting at least the state-I criteria. Of these, 33% had previously been diagnosed with hypertension, and one third of them were taking medication. The remaining 67% were unaware of their hypertensive BP values.

There was an increase in median BP and FPP values across age groups until 50-55 and 55-59 years, respectively (Table 11, p. 53). Regarding undiagnosed diabetes, no clear trend was seen. Waist circumference, BP, and prevalence of hypertension increased among glycemic groups, reaching the peak in the diabetic group (Table 12, p. 54). This group also had the highest percentage of family members suffering from diabetes.

Table 10 Overall characteristics of screening participants (including participants with reported diseases and use of medication)

Group / Variable	All n=382	Female n=264	Male n=118
Age [years]	47.5	48	45.0
	40.0; 54.0	41.0; 54.0	39.0; 53.0
Smoke [yes] [%]	2	0.4	6
Alcohol [yes] [%]	48	47	51
Education			
completed primary [%]	36	39	47
completed secondary [%]	19	18	36
college [%]	36	31	19
Reporting disease [%]	36	36	36
Regular medication [%]	22	24	19
Body mass index [kg/m²]	29.9	30.7	28.3
	28.2; 31.1	29.0; 32.5	27.7; 31.0
Waist circumference [cm]	94.2 (7.1)	92.4 (6.9)	98.0 (6.3)
Diabetic family member [%]	26	29	19
Fasting plasma glucose [mmol/L]	5.5	5.5	5.6
	5.1; 6.1	5.0; 6.1	5.2; 6.3
Normal FPG [%]	51 (73)	54 (74)	44 (69)
Impaired FPG [%]	35 (13)	32 (12)	42 (16)
diabetic FPG [%]	14	14	15
undiagnosed diabetic FPG [%]	62	66	53
Dysglycemia [%]	49 (27)	46 (26)	56 (31)
HbA1c [%, (mmol/mol)]	5.7 (39)	5.7 (39)	6.0 (42)
	5.4 (36); 6.1 (43)	5.3 (34); 6.0 (42)	5.4 (36); 6.3 (45)
normal [%]	42 (70)	45 (76)	37 (58)
pre-diabetic [%]	42 (14)	40 (9)	46 (25)
diabetic [%]	16 (16)	15 (15)	17 (17)
Systolic BP [mmHg]	128.0	127.0	129.0
	117.0; 143.0	115.0; 143.0	119; 143.0
Diastolic BP [mmHg]	86.0	86.0	87.0
	80.0; 93.5	79.0; 92.0	80.0; 96.3
Hypertension type I [%]	24	26	20
Hypertension type II [%]	9	8	10
Hypertension type III [%]	8	7	10
Overall hypertension [%]	41	41	40
undiagnosed hypertension	68	65	71

If not otherwise specified, data are expressed as median and interquartile range; waist circumference is presented as mean and SD; glycemic status based on fasting plasma glucose (FPG) is shown using American Diabetes Association (ADA) and World Health Organization (WHO, shown in parentheses) criteria; dysglycemia was defined by FPG ≥5.6 mmol/L (ADA) or ≥6.1 mmol/L (WHO); HbA_{1c} is shown using ADA criteria; BP: blood pressure, hypertension was defined by having at least one value in stage I, II, or III according to American Heart Association criteria

Table 11 Anthropometric and medical data within different age groups of screened participants

Age group / Variable	30-34 n=34	35-39 n=52	40-44 n=69	45-49 n=72	50-54 n=76	55-59 n=57	≥60 n=27
Body mass index [kg/m²]	29.2	29.2	30.2	30.8	29.7	30.2	30.7
	28.3; 32.2	27.8; 32.0	28.0; 32.1	28.5; 32.8	28.2; 32.0	28.0; 31.5	28.1; 32.6
Waist circumference [cm]	91.9 (7.9)	92.3 (7.1)	93.8 (7.7)	95.4 (7.0)	95.4 (7.0)	94.2 (6.0)	94.1 (7.2)
Fasting plasma glucose [mmol/L]	5.3	5.3	5.4	5.6	5.8	5.6	5.7
	4.7; 5.6	4.8; 5.6	5.0; 6.1	5.1; 6.1	5.2; 6.6	5.1; 6.8	5.3; 6.2
normal [%]	73 (91)	64 (88)	54 (75)	48 (73)	37 (61)	44 (64)	55 (68)
pre-diabetic [%]	24 (6)	30 (6)	29 (9)	35 (10)	45 (21)	40 (20)	36 (23)
diabetic [%]	3	6	16	17	18	16	9
undiagnosed diabetic FPG [%]	100	33	82	58	50	67	50
Dysglycemia	27 (9)	36 (12)	45 (15)	52 (27)	63 (39)	56 (26)	47 (31)
HbA1c [% (mmol/mol]	5.5 (37)	5.6 (38)	5.7 (39)	5.8 (40)	5.8 (40)	5.9 (41)	5.8 (40)
	5.2 (33);	5.3 (34);	5.3 (34);	5.3 (34);	5.6 (38);	5.6 (38);	5.6 (38);
	5.8 (40)	5.9 (41)	6.1 (43)	6.1 (43)	6.3 (45)	6.5 (48)	6.2 (44)
Systolic blood pressure [mmHg]	118.5	122.5	125.0	126.0	131.0	139.0	136.0
	108.5; 128.3	112; 131.8	114.5; 135.5	117.0; 143.0	120.3; 146.0	126.0; 152.5	121.8; 150.5
Diastolic blood pressure	81.0	86.0	84.0	87.0	90.0	86.0	89.0
[mmHg]	77.0; 87.8	80.0; 91.0	78.5; 91.0	81.0; 96.0	82.0; 96.8	79.5; 96.0	78.9; 97.0
Hypertension type I [%]	12	10	12	14	25	35	23
Hypertension type II [%]	0	2	4	9	9	9	9
Hypertension type III [%]	0	4	0	7	8	5	4
Overall hypertension [%]	12	16	16	30	42	49	36

If not otherwise specified, data are expressed as median and interquartile range; waist circumference is presented as mean and SD; glycemic status based on fasting plasma glucose (FPG) is shown using American Diabetes Association (ADA) and World Health Organization (WHO, shown in parentheses) criteria; dysglycemia was defined by FPG ≥5.6 mmol/L (ADA) or ≥6.1 mmol/L (WHO); HbA1c is shown using ADA criteria; hypertension was defined by having at least one value in stage I, II, or III according to American Heart Association criteria

Table 12 Health indicators among glycemic groups (according to ADA criteria)

Group / Health indicator	Normal n=190	Pre-diabetic n=131	Diabetic n=52	Diagnosed diabetes n=20	Undiagnosed diabetes n=32	Treated diabetes n=13
Age [years]	45.0	49.0	49.0	50.0	47.0	53.0
	38.0; 53.0	42.0; 54.0	43.3; 54.0	45.0; 54.0	43.0; 54.0	47.5; 56.0
Body mass index [kg/m²]	29.8	30.2	30.4	30.3	30.4	30.2
	28.1; 32.3	28.1; 32.1	28.6; 31.9	28.4; 32.4	29.0; 31.8	28.0; 32.2
Waist circumference [cm]	92.5 (6.9)	95.5 (7.1)	97.0 (6.3)	97.8 (6.7)	96.5 (6.0)	97.4 (7.9)
Diabetic family member [%]	22	22	54	80	38	92
Fasting plasma glucose [mmol/L]	5.1	5.9	9.2	12.4	8.0	12.2
	4.7; 5.3	5.7; 6.3	7.4; 13.5	8.6; 17.8	7.3; 14.1	7.5; 18.2
HbA1c [% (mmol/mol)]	5.6 (38)	5.8 (40)	7.7 (61)	9.0 (75)	6.8 (51)	8.5 (69)
	5.3 (34);	5.5 (37);	6.6 (49);	7.7 (61);	6.3 (45);	6.3 (45);
	5.8 (40)	6.1 (43)	9.8 (84)	10.1 (87)	8.4 (68)	10.1 (87)
Systolic blood pressure [mmHg]	123.5	130.0	134.0	133.5	135.0	134.0
	114.0; 137.3	120.0; 144.0	123.0; 155.5	122.3; 152.8	123.5; 170.5	123.8; 157.5
Diastolic blood pressure [mmHg]	84.0	89.0	90.0	88.0	95.5	90.0
	78.0; 91.0	80.0; 96.0	84.3; 97.8	80.5; 95.3	85.1; 99.5	80.0; 98.5
Hypertension type I [%]	20	27	31	25	19	23
Hypertension type II [%]	7	12	10	10	9	15
Hypertension type III [%]	6	8	14	5	19	8
Overall hypertension [%]	33	47	55	40	47	46

If not otherwise specified, data are expressed as median and interquartile range; waist circumference is presented as mean and SD; hypertension was defined by having at least one value in stage I, II, or III according to American Heart Association criteria

Table 13 shows results of the non-linear model with SUR. As the overall R^2 values were relatively low, with R^2 ranging between 0.184 and 0.248, the results should be interpreted with caution. Age had a greater effect on systolic BP than on the FPG and HbA_{1c}. Waist circumference had a higher effect on FPG and HbA_{1c} than on blood pressure. A similar trend was seen for BMI. Waist circumference showed a linear association with the dependent variables, whereas BMI showed a non-linear association. Correlations of dependent variables are shown in Table 14. As expected, systolic BP correlated highly with diastolic BP (0.804), and FPG with HbA_{1c} (0.847). Systolic BP showed a medium correlation with FPG and HbA_{1c}, whereas diastolic BP only showed a low correlation.

Table 13 Results of the non-linear model using seemingly unrelated regression, n=291 for predictor age and body mass index, n=290 for predictor waist circumference

	Fasting plasma glucose		**HbA1c**		**Systolic blood pressure**		**Diastolic blood pressure**		**Overall R^2**
Predictor	Co-efficient[c]	*p*	Co-efficient[c]	*p*	Co-efficient[c]	*p*	Co-efficient[c]	*p*	
Age[a]	0.140	0.003	0.177	0.000	0.339	0.000	0.195	0.001	
Age_sq[a]	0.142	0.001	0.098	0.012	0.019	0.765	0.064	0.298	
R^2		0.045		0.048		0.119		0.052	0.184
WC[b]	0.219	0.000	0.221	0.000	0.114	0.047	0.123	0.029	
WC_sq[b]	0.010	0.834	0.047	0.309	0.059	0.325	0.107	0.052	
R^2		0.093		0.086		0.134		0.078	0.248
BMI[b]	0.142	0.003	0.130	0.005	0.008	0.893	0.026	0.682	
BMI_sq[b]	0.162	0.000	0.091	0.051	0.014	0.798	0.061	0.281	
R^2		0.075		0.064		0.119		0.058	0.230

WC:waist circumference, BMI:body mass index, [a]Controlled for sex, [b]controlled for sex and age, [c]standardized, sq:quadratic

Table 14 Correlations of dependent variables controlled for age and sex, all *p*<0.05

	Fasting plasma glucose	**HbA_{1c}**	**Systolic blood pressure**
HbA_{1c}	0.847		
Systolic blood pressure	0.264	0.205	
Diastolic blood pressure	0.197	0.150	0.804

4.1.2 Enrollment rate

After screening for all other inclusion and exclusion criteria, 74 people met all medical inclusion criteria and none of the exclusion criteria. Sixty-one agreed to participate in the intervention study (Figure 11). Two common exclusion factors for people who met the pre-diabetes criterion were having high BP and taking regular medication. Overall, the recruitment rate was 5% starting from the pre-screening phase and 16% starting from the screening phase (after found to have eligible BMI and age).

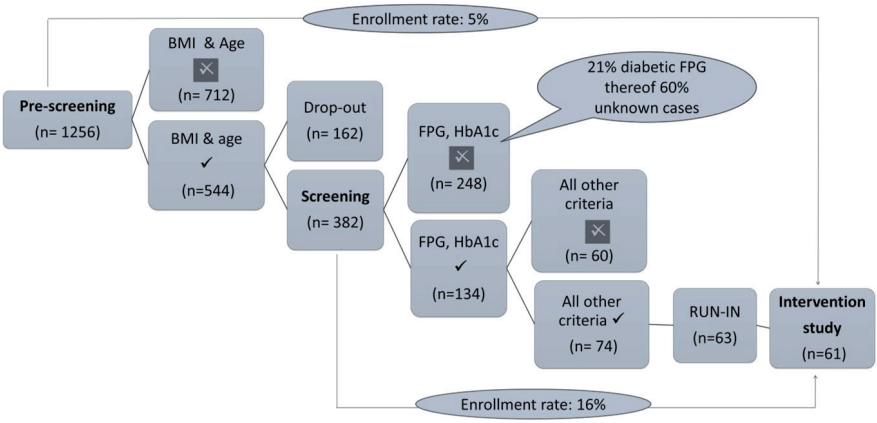


Figure 11 Flow of recruitment procedure with enrollment rates

4.2 Intervention study

Results are presented as either means ± SDs or frequencies. Results are presented for Group 1 and Group 2 as well as for bitter gourd and placebo groups. In the latter, T_1 incorporates data of N_1 and N_3 assessments and T_2 incorporates data of N_2 and N_4 assessments (Figure 12).

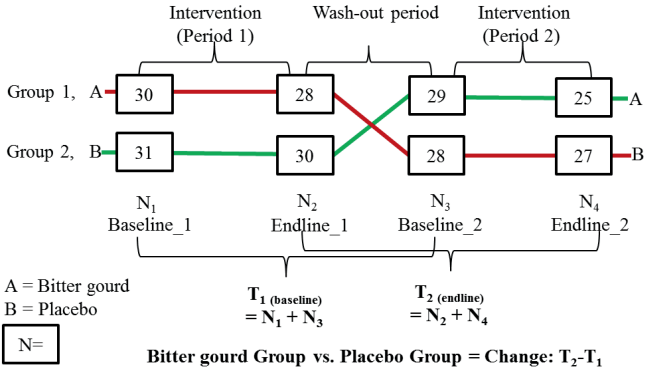


Figure 12 Overview on study design, treatment groups, and number of participants

4.2.1 Study flow chart and participants' characteristics

Sixty-one participants started the study in October 2013, with 52 finishing in March 2014. The dropout rate was 15%. Major reasons for dropout included traveling during the first period and nausea during period 2, which can be found in the CONSORT diagram (Moher *et al.* 2001), Figure 13, p. 58. Dropout was higher within Group 2, which first received placebo and then bitter gourd. Here, four women dropped out due to nausea and vomiting after consumption of bitter gourd sachets during period 2. Among the 52 participants who finished the study, not all had complete data for the endline assessments. Table 15, p. 59, shows baseline characteristics in regard to socioeconomic, demographic, and family-related data in of the overall study population, Group 1, and Group 2. Mean age was 47.5±8.7 for the overall study. The majority were married and had either at least finished primary education or gone to college. Most study participants were working in the business sector or were office workers. Only 4% of the study participants said they smoked and about half said they consume alcoholic beverages. Fifty

percent said they have a family member with high BP and 15% reported having a family history of diabetes.

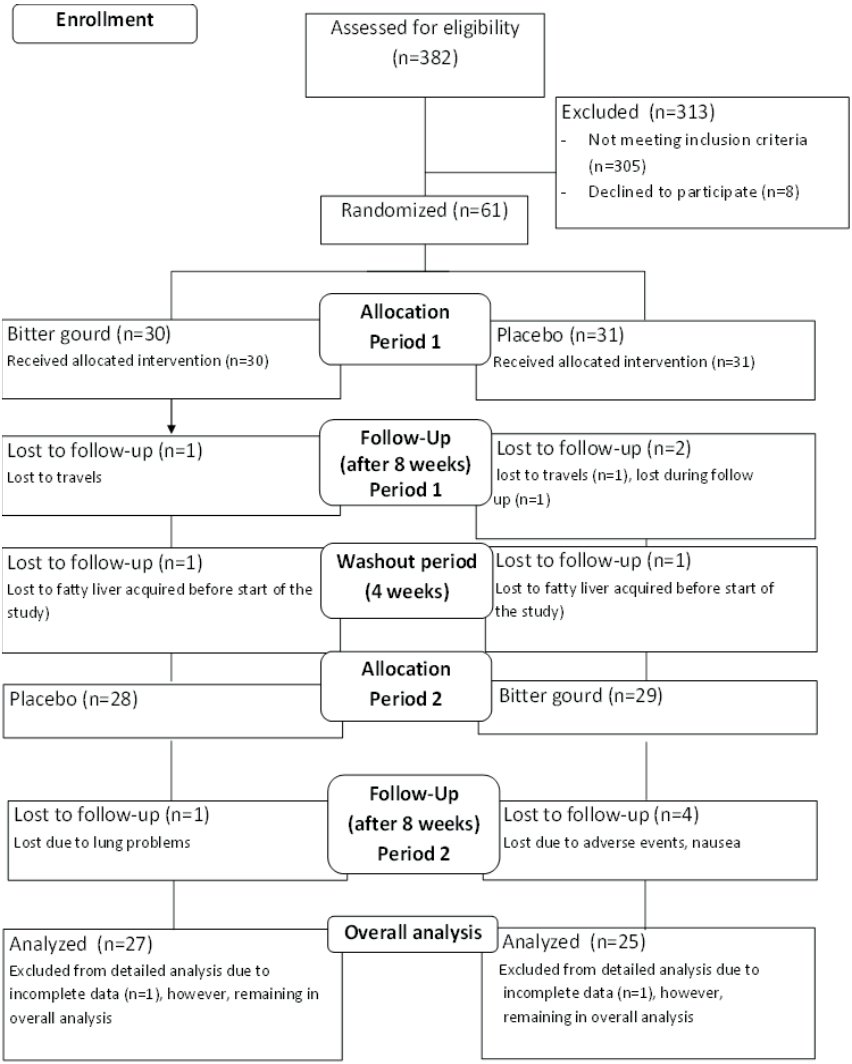


Figure 13 CONSORT study flow diagram of the intervention study

Table 15 Baseline characteristics of intervention study population

Variable \ Group	Overall (n=52)	Group 1 (AB) (n=28)	Group 2 (BA) (n=24)
Age	47.5 ± 8.7	48.21 ± 8.4	46.63 ± 9.1
Mean household size	4.4 ± 2.7	4.5 ± 3.1	4.1 ± 2.1
[%] female	54	54	54
Marital status [%]			
Single	15	14	17
Married	67	68	65
Divorced/separated	4	7	0
Widowed	14	11	17
Religion [%]			
Christian	90	86	95
Muslim	10	14	5
Educational status [%]			
No formal education	2	4	0
Finished primary	38	43	33
Finished secondary	13	14	13
College	35	25	46
Other	12	7	4
Occupation [%]			
Farmer	6	11	0
Business sector	27	30	25
Student	6	7	4
Teacher	10	7	13
Nurse	6	11	0
Police officer	8	4	13
Office workers or other	37	30	45
Motorized transportation to work [%]	56	52	61
Smoking [%]	4	4	4
Drinking alcohol [%]	52	39	67
Family member with diabetes [%]	15	18	12
Family member with hyptertension [%]	50	46	54

As shown in Table 16, there were no statistically significant differences between Group 1 and Group 2 at baseline N_1. Unlike the HbA_{1c} values, mean FPG values of both groups were no longer in the pre-diabetic range. There was a significant drop in FPG between the screening and the start of the intervention study (chapter 4.2.4). In addition, FPG levels from the venous blood samples were lower than FPG levels from the capillary blood samples. Results of capillary FPG levels during the intervention study are not shown. They served as a control during the regular checkup visits. At baseline N_3, Group 1 started with a significantly lower FPG level. All other variables did not differ.

Table 16 Baseline values of treatment-sequence groups at both baseline assessments

	Period 1			Period 2		
Group / Variable	Group 1 (AB)	Group 2 (BA)	*p*	Group 1 (AB)	Group 2 (BA)	*p*
BMI [kg/m²]	29.1 ± 2.0	30.2 ± 2.5	n.s.	29.5 ± 2.1	30.2 ± 2.8	n.s.
FPG [mmol/L]	5.27 ± 0.44	5.40 ± 0.53	n.s.	4.98 ± 0.49	5.39 ± 0.61	0.039*
HbA_{1c} [%]	5.85 ± 0.43	5.85 ± 0.43	n.s.	5.86 ± 0.39	5.89 ± 0.43	n.s
Insulin [µU/mL]	23.9 ± 16.2	25.0 ± 17.1	n.s.	27.5 ± 16.1	26.6 ± 16.1	n.s.
HOMA-Index	6.07 ± 4.51	6.60 ± 4.41	n.s.	6.03 ± 3.38	7.50 ± 4.14	n.s.
Chol [mmol/L]	4.26 ± 0.91	4.49 ± 0.98	n.s.	4.10 ± 1.22	4.42 ± 0.77	n.s.
HDL [mmol/L]	0.95 ± 0.35	0.91 ± 0.24	n.s.	0.91 ± 0.31	0.85 ± 0.25	n.s.
TG [mmol/L]	1.70 ± 0.94	1.32 ± 0.55	n.s.	1.76 ± 0.71	1.54 ± 0.40	n.s.
Systolic BP [mmHg]	120.7 ± 15.4	122.5 ± 16.2	n.s.	115.5 ± 16.3	116.4 ± 13.1	n.s.
Diastolic BP [mmHg]	82.5 ± 12.4	83.9 ± 9.0	n.s.	79.8 ± 10.9	80.9 ± 8.3	n.s.

BMI: body mass index, FPG: fasting plasma glucose, HOMA: Homeostasis Model Assessment, Chol: cholesterol, HDL: high density lipoprotein, TG: triglycerides, BP: blood pressure, n.s. non-significant, *Two-Samples T-Test, n: varied between parameters as follows: in Group 1: BMI (n=26), FPG (n=24), HbA_{1c} (n=26), insulin and HOMA-Index (n=25), Chol, HDL, and TG (n=26), systolic and diastolic BP (n=25), in Group 2: BMI (n=24), FPG (n=20), HbA_{1c} (n=24), insulin and HOMA-Index (n=21), Chol and HDL (n=24), TG (n=23), systolic and diastolic BP (n=25)

4.2.2 Effects on fasting plasma glucose, HbA_{1c}, and insulin

Figure 14 shows the course of FPG in Group 1 and Group 2. There was a statistically significant difference between Group 1 and Group 2 at assessment N_2 (endline_1) with a significantly lower FPG level after bitter gourd supplementation than after placebo (t(44)=-2.105, *p*=0.041). As mentioned above, FPG differed between groups at assessment N_3 (baseline_2) (t(44)=-2.125, *p*=0.039). During the washout period, there was a decrease in both groups that was not statistically significant. This decrease may be explained by a reduced food intake by study participants in the absence of supplementation. However, a change in food intake among participants during the washout period was not assessed to address this issue.

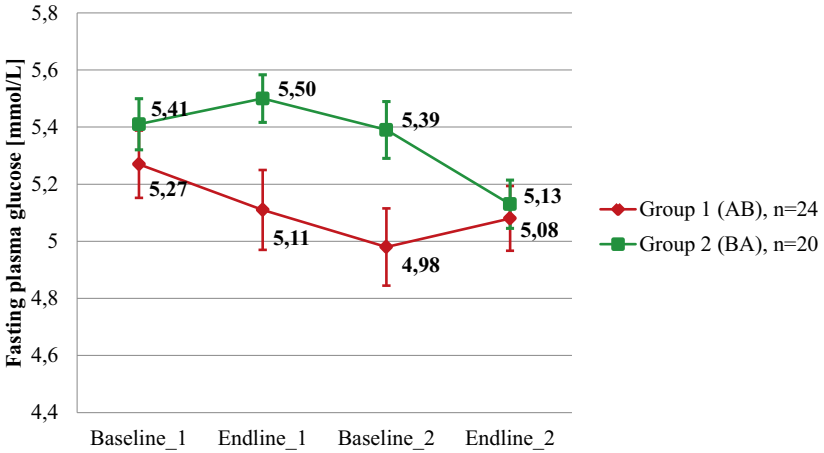


Figure 14 Course of fasting plasma glucose (mean±SE) in Group 1 and Group 2

Both the CROS analysis (t=-2.23, *p*=0.031, r=0.326) revealed a significant difference in the change of FPG between the bitter gourd group and placebo group. There was a decrease in the bitter gourd group and an increase in the placebo group. Overall, the treatment difference was 0.31 mmol/l (5.6 mg/dl). This is lower than the expected clinically relevant difference of 0.56 mmol/l (10 mg/dl). Although the calculated sample size of 54 was not achieved, the current sample size of 44 achieved a power of 0.82, with a medium-to-large effect size Cohen's d of

0.62. The significant treatment effect was also proven by results of the general linear mixed model (Table 17).

Table 17 Results of the general linear mixed model with change of FPG (T_2-T_1) as dependent variable (n=88)

Source	Numerator df	Denominator df	F	*p*
Intercept	1	84	1.524	0.220
Treatment	1	84	6.946	0.010
Carry-over	1	84	0.158	0.692
Period	1	84	0.212	0.647

Estimates of Fixed Effects

Parameter	Estimate	Std. Error	df	t	*p*	95% Confidence Lower bound	95% Confidence Upper bound
Intercept	-0.369167	0.298994	84	-1.235	0.220	-0.96375	0.22541
Treatment	0.310167	0.117687	84	2.636	0.010	0.07613	0.54420
Carry-over	-0.046833	0.117687	84	-0.398	0.692	-0.28087	0.18720
Period	-0.054167	0.117687	84	-0.460	0.647	-0.28820	0.17986

FPG: fasting plasma glucose

The change in FPG differed between subjects (Figures 15-18, p. 63-64). The participant numbers on the x-axis of Figure 15 correspond to the numbers on the x-axis of Figure 16, p. 63, whereas those in Figure 17 correspond to those in Figure 18, p. 64. Not all subjects had a decrease in FPG during bitter gourd supplementation. The change in FPG had a range from -1.75 to 0.92 mmol/L. More participants in Group 1 responded to bitter gourd supplementation than in Group 2. As seen in Figures 15 and 17, the drop in FPG between baseline and endline tended to be greater with a higher baseline FPG level. This observation was also proven in the general linear mixed model, where baseline FPG level had a significant effect on the outcome of endline FPG level.

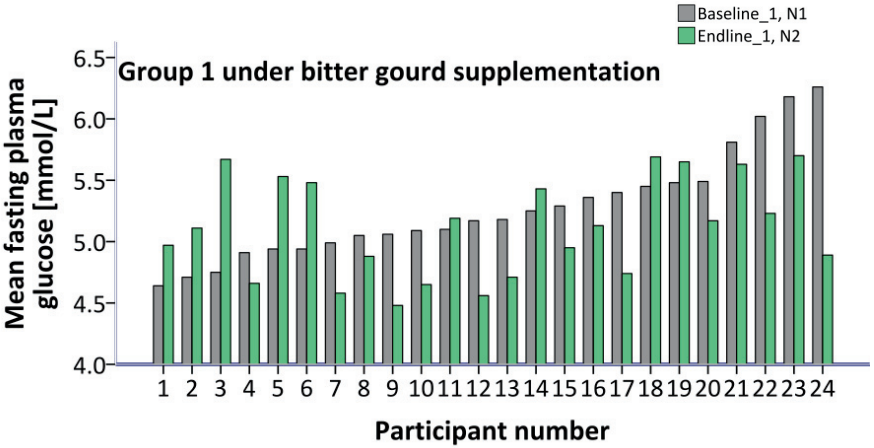


Figure 15 Mean fasting plasma glucose levels of Group 1 at baseline_1 and endline_2

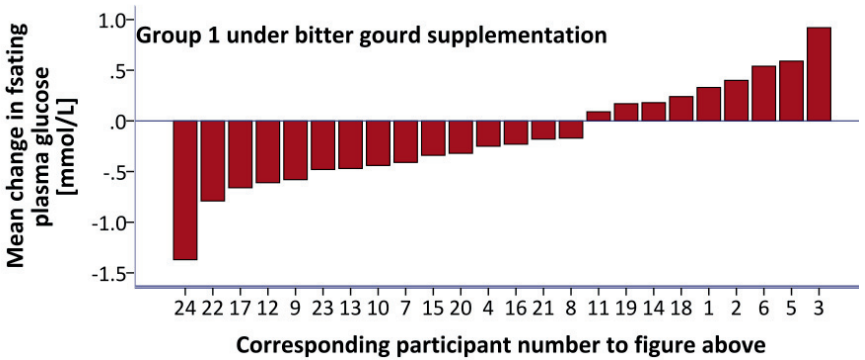


Figure 16 Mean change of fasting plasma group of participants of Group 1 in period 1

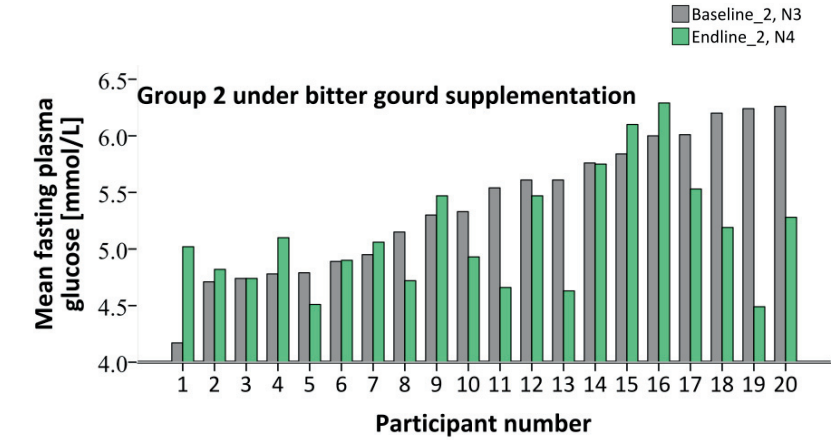


Figure 17 Mean fasting plasma glucose values of Group 2 at baseline_2 and endline_2

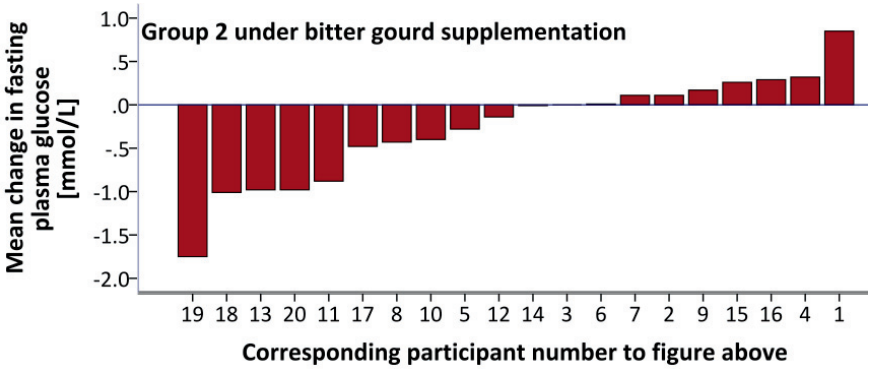


Figure 18 Mean change of fasting plasma glucose in participants of Group 2 in period 2

To control for changes in food intake during the study period, a FFQ was assessed during a run-in period and at endline_2. Results of two FFQs and derived food variety scores were available for 48 participants. Food variety scores did not differ between run-in and endline assessment (51.8±11.3 vs. 50.7±11.4). During the regular checkup questionnaires, around 3-5% of participants said they changed food intake during the preceding week. Some participants increased their intake, whereas others decreased their intake. The most common reason given for a change in food intake was traveling for a business trip or festivities. The physical activity questionnaire was used to check whether participants changed their sports activities during the intervention study. At run-in, 31% said they engaged in sports. At endline, 27% said they engaged in sports. During the regular checkup questionnaire, 2-7% of participants reported changes in physical activity during the previous week. The changes included either more or less physical activity during, for example, work, household chores, and recreation.

In regard to the effect on HbA_{1c}, there was no statistically significant difference between the bitter gourd group and placebo group, despite a tendency for it to decrease in the bitter gourd group (Table 19, p. 67). The same was true for insulin levels. Both Group 1 and Group 2 started with relatively high insulin levels (Table 18, p. 66). A Homeostasis Model Assessment (HOMA) index was calculated (Matthews *et al.* 1985). Based on a cut-off score of ≥2.5 (Muniyappa *et al.* 2008), around 40% of participants were classified as having insulin resistance or severe insulin resistance with values similar to those among diabetes mellitus patients. However, this calculation does not include consideration of individual BMIs of participants. Insulin values were also classified using cut-offs provided by the KCRI laboratory. According to theses cut-offs, almost two thirds were classified as having normal insulin levels.

Table 18 HOMA-Index and laboratory-based cut-offs for insulin resistance at baseline 1

Group / Category	Group 1 (AB) n=25, [%]	Group 2 (BA) n=21, [%]
HOMA-Index		
Normal insulin sensitivity (<2.5)	17	15
Insulin resistance (≥2.5)	46	40
Severe insulin resistance (>5.0)	37	45
KCRI laboratory cut-offs		
Normal (2-25 [µU/mL])	67	60
High (≥25 [µU/mL])	33	40

4.2.3 Effects on blood lipids, anthropometrics, and blood pressure

There were no significant differences between the bitter gourd group and the placebo group with regard to blood lipids, BMI, and BP (Table 19, p 67.). Mean values of TG and Chol were within normal ranges. Both tended to decrease in the bitter gourd group and increase in the placebo group, although the trends were not statistically significant. In contrast, HDL tended to decrease in the bitter gourd group and increase in the placebo group, although the trends were not statistically significant.

Body mass index was similar in both groups before and after treatment. Both systolic and diastolic BP tended to decrease in the bitter gourd and placebo groups. There was a significant decrease in systolic BP between screening and the start of the intervention study in the overall study group (chapter 4.2.6) and within Group 1 and Group 2 during period 1 (data not shown). As some participants reported an intake of medication during the week preceding assessments of venous blood samples, outcome parameters might have been influenced. Intake of medication was lower at both endline assessments, with 39% (n=21) taking medication at T_1, and 17% (n=9) at T_2. Reported medications included cold medicine and pain killers.

Table 19 Mean values and changes (±SD) of treatment groups before and after treatment

Treatment / Variable	Bitter gourd T_1	T_2	Change	Placebo T_1	T_2	Change	Treatment difference	n	*p*
FPG [mmol/L]	5.33±0.52	5.12±0.45	-0.21±0.56	5.17±0.54	5.27±0.56	0.10±0.53	0.31	88	0.01*
HbA1c [%]	5.87±0.43	5.81±0.34	-0.05±0.27	5.86±0.40	5.86±0.41	0.00±0.31	0.05	100	n.s.
Insulin [µU/mL]	25.08±15.94	26.01±14.82	0.91±6.21	26.39±16.51	26.25±14.47	-0.13±6.52	1.04	92	n.s.
Chol [mmol/L]	4.33±0.85	4.25±0.83	-0.07±0.67	4.29±1.12	4.38±1.05	0.09±0.78	0.16	100	n.s.
HDL [mmol/L]	0.90±0.30	0.87±0.36	-0.03±0.19	0.91±0.28	0.93±0.30	0.02±0.15	0.05	100	n.s.
TG [mmol/L]	1.61±0.72	1.57±0.53	-0.05±0.67	1.57±0.69	1.70±0.63	0.14±0.56	0.19	98	n.s.
BMI [kg/m²]	29.6±2.5	29.6±2.4	0.02±0.6	29.8±2.3	29.7±2.4	-0.1±0.5	0.12	102	n.s.
Systolic BP [mmHg]	118.9±14.2	116.5±14.2	-2.4±11.3	118.9±16.5	116.3±12.8	-2.3±10.8	0.1	100	n.s.
Diastolic BP [mmHg]	81.8±10.5	80.1±9.4	-1.8±7.8	81.7±10.1	79.8±8.9	-1.9±6.4	0.1	100	n.s.

FPG: fasting plasma glucose, Chol: cholesterol, HDL: high density lipoprotein, TG: triglycerides, BMI: body mass index, BP: blood pressure, n.s. non-significant, *general linear mixed model

4.2.4 Reported adverse events and side effects

The most-reported side effects were loose stool, diarrhea, flatulence, stomach rumbling, nausea, and vomiting. These side effects were reported by the bitter gourd group more often than the placebo group (mean numbers per side effect were n=9 vs n=5 persons). However, it is difficult to establish a clear causal relationship between the consumption of bitter gourd and the side effects, as the sachet contents were consumed after the main meal, usually dinner. Therefore, side effects could have also been related to food or beverage intake, in addition to other factors such as colds, malaria, or intake of medication. Prior to the study period, 17% (n=9) reported adverse events, such as headache, stomach pain, nausea, and flatulence. During the period 2, four female participants dropped out due to nausea and vomiting after consumption of bitter gourd. One person was excluded from the study after diagnosis of fatty liver during the washout phase. The participant had elevated GPT levels at baseline in period 1 and was referred to a doctor for further assessment. The participant was kept in the study until endline in period 1, at which point GPT was still elevated. The presence of high GPT at the beginning implies that the intervention had no role in causing fatty liver and was acquired before the intervention period. The participant tested negative for hepatitis infections. An ultrasound revealed a fatty liver. The participant was counseled on a healthy lifestyle, excluded from the study, and checked again for GPT levels at the end of the study. At that point, GPT levels had returned to normal. The remaining dropouts were caused by traveling and, in one case, by follow up for lung problems acquired during the washout period. There were no serious adverse events during the study period. During the study period, adverse events included perceived side effects and reports of colds, malaria episodes, headaches, nausea, diarrhea, worm infections, body fatigue, and muscle pain. On average, 14% (n=7) took some kind of medication, such as pain or cough medication, during the week prior to the regular checkup.

The parameters glutamate pyruvate transaminase and plasma creatinine were assessed to monitor effects on liver and kidney functions. GPT and creatinine analysis excluded the results from one participant each, as their values were more than 3 SD higher than the mean. One participant with high GPT levels tested negative for hepatitis infections and received counseling on a healthy lifestyle. At the end of the study, his GPT levels were within the normal range. Further, his high levels of GPT during the first two assessments may have been due to

intake of antibiotics and pain killers during the week prior to venous blood sampling. The elevated creatinine level of one participant may have been due to a high intake of protein. All other values of that participant were within normal ranges. Overall, there were no significant differences in GPT and creatinine levels between groups at both baseline and endline (Table 20).

Table 20 Creatinine and glutamate pyruvate transaminase values (mean±SD) and before and after treatment

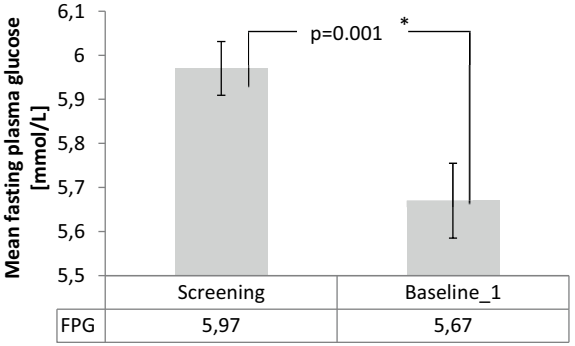
Treatment / Variable	Bitter gourd			Placebo				
	T1	T2	Change	T1	T2	Change	n	*p*
Creatinine [µmol/L]	78.9±18.5	80.9±17.7	2.0±15.8	74.5±16.6	81.8±18.5	7.6±13.6	98	n.s.
GPT [IU/L]	25.1±10.6	25.4±12.1	0.3±11.4	25.6±10.6	24.1±7.8	-1.4±7.8	98	n.s.

GPT: glutamate-pyruvate transaminase, n.s.: not significant

4.2.5 Glucose-lowering effect between screening and baseline assessment

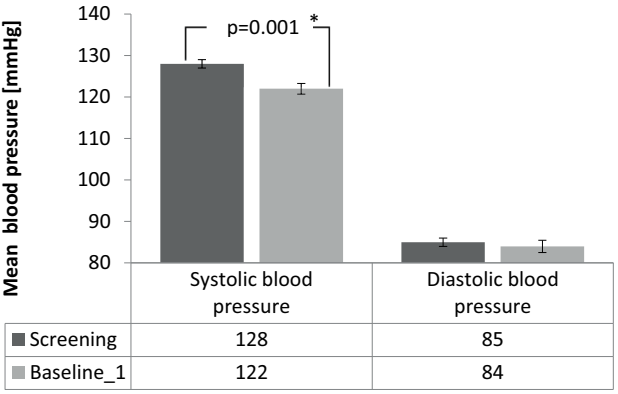
The screening for the intervention study took place between July and October 2013. The intervention study started in mid and late October 2013. Between these two timeframes, there was a significant decrease in FPG (Figure 19, p. 70) (Wilcoxon Signed Rank Test, z=-3.276, *p*=0.001) measured by capillary blood samples. The difference of 0.3 mmol/L of FPG was similar to the treatment difference of 0.31 mmol/L in the intervention study.

Systolic BP significantly decreased during the intervention study (Figure 20, p. 70), (paired t-test, t(51)=3.845, *p*=0.001). Diastolic BP also decreased, but it was not statistically significant. During the screening procedure, counseling on a healthy lifestyle was provided, if requested. No assessment of changes was performed during the time between the screening and the start of the intervention study.



*Wilcoxon Signed Rank Test

Figure 19 Fasting plasma glucose of overall study group at screening and baseline_1



* Paired Samples T-Test

Figure 20 Blood pressure of overall study group at screening and baseline_1

5. Discussion

The discussion is divided into two major sections according to the results. The first section elucidates implications of health aspects and problems which were found during the screening process. Further, it compares the current enrollment rate to other studies and opportunities for health promotion activities. The second section discusses the observed hypoglycemic effect of bitter gourd with findings of other studies, describes glucose-lowering mechanisms and other bitter gourd related effects on blood lipid parameters and obesity. To illustrate the complexity of causes of and challenges in regard to type 2 diabetes mellitus, the conceptual framework of malnutrition by United Nationals International Children's Emergency Fund (Unicef) was modified according to findings of the current studies and other research groups. Limitations and conclusion are stated for the recruitment procedure and intervention study together.

5.1 Implications of the recruitment procedure

5.1.1 Obesity, hypertension and elevated blood glucose values

Recruitment for pre-diabetic volunteers was divided into two stages, a pre-screening phase and a screening phase, and was communicated via different channels. Due to word-of-mouth communication, 26% of pre-screened participants were pre-screened without prior attendance at information sessions, but were instead referred by already-pre-screened people. In the pre-screening sample, rates of overweight and obesity were 37% and 32%, respectively. However, as people with increased body weight were encouraged to participate in the recruitment procedure, higher rates of overweight and obesity were expected. In the most recent Tanzanian Demographic Health Survey (TDHS) of 2010, 35% and 24% of women in the Kilimanjaro Region were overweight or obese, respectively. The TDHS did not report any data for men (National Bureau of Statistics *et al.* 2011). As obesity is linked to an increased risk of non-communicable diseases and negative outcomes (Dixon 2010), the high rates of obesity, especially of classes two and three in the current study, are a major health threat for that area. In the current study, obese participants had significantly higher BP values than normal-weight participants. Although sex was not assessed during pre-screening, an analysis of a subsample (KCRI-pre-screening sample, data not shown) showed that women were three times more likely to be obese than male participants. This phenomenon was also seen in a study conducted in Mwanza District,

where the obesity prevalence of women was 22% and of men was 7% in town settings (Kavishe *et al.* 2015).

In the current setting, eligible BMIs in the overweight and obese ranges were more common among more office workers and teachers than among people pre-screened at religious institutions. This may be linked to a more sedentary lifestyle due to office jobs or jobs with low physical activity (Agrawal *et al.* 2013). Therefore, activities promoting general health might be necessary to address health-related issues specific to subgroups such as office workers and women. However, another study detected a high BMI as a predictor for a sedentary lifestyle (Mortensen *et al.* 2006). In regard to increased BMI and a trend toward non-agricultural jobs in Tanzania (International Labour Office 2009), possibilities to engage in physical activity outside of work have to be evaluated.

In the current study, BMI increased with age until the age group of 40-49 years, similar to results reported in the TDHS (National Bureau of Statistics *et al.* 2011). Systolic BP increased with age. Diastolic BP peaked at the age group of 40-49. Both were correlated with BMI, although diastolic BP was more highly correlated with BMI than systolic BP. Other studies have demonstrated age- and BMI-related increases in systolic and diastolic BP (Mungreiphy *et al.* 2011) and as predictors, independently from each other, for hypertension (Gebreselassie *et al.* 2015). Overall, 30% of pre-screened participants were classified as hypertensive, which is similar to the WHO's age-standardized estimate of 29% (WHO 2014). The majority was unaware of their hypertensive BP values, which was also seen in other settings (Kavishe *et al.* 2015) and needs to be addressed in future health programs.

Although the screening sample was not representative and had no diagnostic character, there were high rates of pre-diabetic and diabetic FPG values (35% and 14%, respectively) and HbA_{1c} values (42% and 16%, respectively), according to ADA criteria. Around 60% were unaware of their diabetic FPG levels, which was lower than the estimate of 67% in Sub-Saharan Africa (IDF 2015). In other studies, rates of undiagnosed diabetes ranged from 18% to 62% (Heianza *et al.* 2012; Kavishe *et al.* 2015; Mayega *et al.* 2013). The overall high prevalence of diabetes among the screening sample can be explained by the high number of diabetics who came to the screening, with many reporting that they thought they were coming to a new diabetes clinic offering free measurements. In the subgroup of treated diabetic patients, median HbA_{1c} was

8.5% (69 mmol/mol), higher than the recommended target level of 7% (65 mmol/mol) for glycemic control among diabetic patients (ADA 2014). In addition, FPG and HbA_{1c} levels among people with diabetic FPG (treated and untreated; known and unknown) were high. This, together with the high levels of hypertension, indicates that urgent action is needed to improve health outcomes among people afflicted by diabetes.

As seen in other studies (Mayega *et al.* 2014; Mayega *et al.* 2013; Bao *et al.* 2015; Xu *et al.* 2013), pre-diabetic prevalence rates varied between ADA and WHO criteria. In the current study, ADA criteria resulted in a 2.7 times higher prevalence rate than WHO criteria. The WHO had previously stated that lowering the threshold for IFG from 6.1 mmol/L to 5.6 mmol/L would result in a higher rate of pre-diabetes with a lack of evidence for better health outcomes (WHO 2006). The prevalence of 35% according to ADA was more than three times higher than the national prevalence of 10.3% of pre-diabetes defined as IGT (IDF 2013). According to WHO criteria, prevalence of pre-diabetes was 12%. The higher rates may be due to the tailored screening of people with higher BMI and age, as well as differences in IFG and IGT. People with IFG may not necessarily have IGT, and vice versa, which may be due to different pathological pathways and other factors (Perreault *et al.* 2014). In a study by Zhang et al., isolated IFG was prevalent among 28% of study participants, whereas 5.1% had isolated IGT and 10.3% had both IFG and IGT (Zhang *et al.* 2015). In a study by Chilelli et al., isolated IFG was seen in 27.1%, isolated IGT in 6.8%, and both in 4.6% (Chilelli *et al.* 2014). Both applied ADA cut-off values for IFG, which may explain the higher rates of pre-diabetes based on FPG than based on glucose tolerance. The current study did not assess glucose tolerance. Measurement of glucose tolerance is not always feasible in resource-poor or work settings, as it is cumbersome and time consuming for the participant, especially in a screening setting (Anand *et al.* 2003; Mayega *et al.* 2014) . In the current screening, which had no diagnostic character, the measurement of FPG to define glycemic status was quick and easily administered by health staff.

Yudkin and Montori (2014) expressed concerns about the new ADA cut-offs and the subsequent increase in pre-diabetes diagnoses, as well as the overall concept of categorizing people as pre-diabetic. They argue that it diverts attention from high risk people or diabetic patients who need medical attention (Yudkin *et al.* 2014). Rates of pre-diabetes may be even higher when an HbA_{1c} cut-off of 5.7 to 6.4% is applied (Yudkin *et al.* 2014), which was also the

case in the current screening in which 42% of participants had pre-diabetic HbA_{1c} values compared to 35% for IFG (ADA criteria) or 12% for IFG (WHO criteria). These results were also seen in other studies, where rates of pre-diabetes using HbA_{1c} measures were higher than using measures of FPG or 2-hour plasma glucose (Mayega *et al.* 2014; Botana Lopez *et al.* 2012). However, some other studies showed comparable rates (Costa *et al.* 2013), and some missed cases or showed lower rates when applying ADA defined HbA_{1c} cut-offs (Bhansali *et al.* 2012; Zhou *et al.* 2010).

In the current screening, diabetic glucose had the highest concordance between HbA_{1c} and FPG, although the overall Krippendorff's alpha was low (0.351). In a cross-sectional study at a primary care setting in Spain (Costa *et al.* 2013), HbA_{1c} measurement revealed a significantly lower diabetes prevalence (3.2%) compared to 2-hour plasma glucose testing (9.2%), but was similar to FPG (3.1%). In a population-based survey in a rural district of Uganda, diabetes prevalence rates were 4.8% according to FPG and 11.3% according to HbA_{1c}. Despite the low agreement between HbA_{1c} and FPG, they detected a high agreement among negatives (normo-glycemic FPG and normal HbA_{1c}) (Mayega *et al.* 2014). Specifying universal cut-off points for HbA_{1c} may be difficult due to ethnic differences, with higher levels observed among people of African origin (Selvin *et al.* 2011; Ziemer *et al.* 2010), as well as other influencing factors (Dubowitz *et al.* 2014). However, it has been argued that HbA_{1c} is a valid predictor for diabetes, including undiagnosed cases, but should not be used to identify pre-diabetes (WHO 2011).

In regard to risk factors for increased glucose or BP values, the current study showed similar results to other assessments (Veghari *et al.* 2014; Patil *et al.* 2012; Okosun *et al.* 1998; Davidson *et al.* 2014) with WC and BMI being predictors for FPG and BP. The association between WC and dependent variables (FPG, HbA_{1c}, BP) was linear, whereas it was non-linear for BMI. The current study had an upper BMI limit of 35 kg/m^2 whereas a higher limit would be needed to assess this issue of a non-linear association between BMI and FPG and BP. In a study in Brazil, mean BMI did not differ between glycemic groups, but WC was significantly higher among the pre-diabetic group than the normo-glycemic group (Franco *et al.* 2014). In another study, obese people were two times more affected by dysglycemia than normal-weight people (Mayega *et al.* 2013). The measurement of WC as a low cost and noninvasive method might serve as a good screening tool to assess risk for dysglycemia in that region.

In the current study, there was no difference in BP or glycemic status between alcohol consumers and non-consumers. Overall, alcohol consumption was similar to national data (WHO 2014). Smoking rates were considerably lower with 6% and 0.4% among men and women, compared to national data of 28% and 4%, respectively (WHO 2014). Thus, no association with tobacco use could be calculated. A study by Mayega found no association of abnormal glucose regulation with sex, age group, hypertension, tobacco use, or harmful alcohol use (Mayega *et al.* 2013).

5.1.2 Comparison of enrollment rates and health related activities

The overall enrollment rate was 5% from the pre-screening phase and 16% from the screening phase. The 16% corresponds to 13-14 participants per month. Several studies for the Diabetes Prevention Program were conducted in working environments and resulted in recruitment rates of 10-11 participants per month (Ackermann *et al.* 2008), 14 participants per month (Blackwell *et al.* 2011), 45 participants per month (Taradash *et al.* 2015), and 59 participants per month (Amundson *et al.* 2009). Although 74 screened participants were eligible for the current intervention study, only 61 started the trial. Queries for non-participation were not conducted. In other diabetes-related programs, a common reason given for non-participation was time conflicts (Toobert *et al.* 2002; Taradash *et al.* 2015). The recruitment rate might have been higher with less strict BMI and age criteria. However, this would have lowered the homogeneity of the sample population of the subsequent intervention study.

Communication for scheduling appointments and reminding participants to fast in advance was done via phone calls and text messages. Since almost everyone owned a cell phone or had a relative or friend with a cell phone, this proved to be an effective and convenient mode of communication that could be used in future health programs. Public and private institutions were generally open to collaboration and allowed members of the research team to introduce themselves and the project, and also allowed their workers to participate in the screening. In addition, support was provided through official channels such as the Regional Medical Office. The positive behavior shows that private and public institutions are open to health-related issues and might be approached for future health programs and activities.

Whether screening for diabetes will be feasible in that region needs to be discussed

among health and policy institutions. It has been argued that screening for diabetes is not justifiable, as it does not meet all criteria for disease screening (Diabetes Care 2002) as defined by WHO (Wilson, J. M.G. *et al.* 1968). One major criticism is that screening should only be done if medical treatment is available (Wilson, J. M.G. *et al.* 1968; National Cancer Control Policy Australia 2015). Assessments indicate that there are insufficient medical supplies and treatment facilities in Tanzania (Peck *et al.* 2014a; Ministry of Health and Social Welfare, Tanzania 2013; Robertson *et al.* 2015), which would speak against performing screening. However, because the progression of pre-diabetes to diabetes mellitus type 2 and the outcomes of diabetes mellitus type 2 might be modified with lifestyle changes (Burr *et al.* 2010; Sato *et al.* 2007), especially increased physical activity, a screening of pre-diabetes or diabetes may be worthwhile. Promotion of a healthy lifestyle and related activities should be strived for generally, but could also be conducted with the help of screening, as people might be more motivated to change eating and physical activity habits after they know their own health status. In the current setting, FPG significantly dropped among some study participants from the time point of the screening (5.97 (±0.47) mmol/L) to the start of the baseline study (5.67 (±0.61) mmol/L). During the screening process, counseling on a healthy lifestyle was provided to participants if requested. The provided counseling may have led to a change in behavior and a drop in FPG. Nevertheless, in regard to the region's high levels of elevated BP and glucose levels, health promotion strategies should be established in addition to screening activities. Such promotion, screening, and education activities are already incorporated at an exhibition of KCMC during the World Diabetes Day (Figure 21 and Figure 22, both p. 77), but need to be extended.

Figure 21 Members of the public obtaining educational material on diabetes at the KCMC exhibition during Diabetes Day 2013

Figure 22 Measurement of fasting plasma glucose and HbA_{1c} at KCMC exhibition during Diabetes Day 2013

5.2 Intervention study effects

5.2.1 Glucose lowering effect compared to other studies

In the current cross-over study, bitter gourd supplementation had a glucose-lowering effect on FPG compared to placebo. The effect was associated with the baseline FPG level. Participants with higher FPG levels at baseline showed a greater change in level than those with lower FPG levels. Therefore, bitter gourd may be more effective in lowering glucose levels when they start at high values.

Although participants were screened for pre-diabetes, some had normal FPG levels at baseline. This may have affected the outcome of the study and reduced the glucose-lowering effect of bitter gourd. Although not statistically significant, the decrease during the washout period may be explained by a reduced food intake during the absence of a supplementation. However, no data was collected during the washout period. Fewer participants responded to bitter gourd treatment in period 2 than in period 1 (Figure 15, p. 63 and Figure 17, p. 64). This may also be related to the lower FPG levels at baseline_2 compared to baseline_1.

With regard to HbA_{1c} and insulin, no differences were seen between bitter gourd and placebo groups. Overall, insulin levels and insulin resistance based on the HOMA index seemed to be high among the study participants. As BMI was not considered in the current calculation of HOMA-IR scores, the actual cut-off point to classify insulin resistance may be higher. HOMA-IR cut-off values do not only change with BMI, but also vary between populations (Gayoso-Diz *et al.* 2013; Stern *et al.* 2005). Further, insulin values can vary depending on the laboratory tests applied (Manley *et al.* 2008). Insulin resistance according to the HOMA index and laboratory base cut-offs differed in the study population. This difference and the high insulin levels need further investigation in future studies.

The current study showed a glucose-lowering effect of bitter gourd among pre-diabetics. Most other studies that examined anti-diabetic effects of bitter gourd were performed with diabetes mellitus patients, who had higher baseline FPG and HbA_{1c} levels. Thus, comparisons to the current study results have to be made cautiously.

The current study used whole fruit powder mixed with water as a supplementation. Whole bitter gourd fruit was also used in other studies, either in tablet form (John *et al.* 2003),

capsule form (Tsai *et al.* 2012; Srivastava *et al.* 1993), or aqueous extract form (Srivastava *et al.* 1993). John *et al*. (2003) examined the effects of a supplementation of 6 g dried powder per day for four weeks as an adjunct therapy for 26 diabetic patients. Although study participants had higher baseline FPG levels of 8.33±1.49 mmol/L compared to the current setting, and the dosage was more than two times higher, there were no statistically significant effects on FPG, postprandial plasma glucose, and fructosamine levels, compared to placebo. The authors assume that patients might have maintained their normal dietary regimens or intake of OAD (John *et al.* 2003).

Srivastava *et al*. (1993) examined effects of a supplementation of 100 mL aqueous extract per day, equivalent to 100 g cooked fruit in 200 mL water, for seven weeks among patients with mild to severe diabetes. No information was provided about concomitant treatment with hypoglycemic agents. The supplementation significantly dropped postprandial glucose levels by 54%, and decreased HbA_{1c} levels from a baseline of 8.37±0.39% to 6.95±0.46%. In addition to supplementation with the aqueous extract, five diabetic patients were supplemented with 5 g fruit powder per day in tablet form for three weeks. After this supplementation, no anti-diabetic effect was observed (Srivastava *et al.* 1993).

Another study, which included the whole fruit of bitter gourd, was conducted by Tsai *et al.* (2012) with participants who met at least three criteria for metabolic syndrome. Here, 4.8 g of fruit powder capsules per day were consumed by eligible participants over three months. The authors reported an improvement in logHOMA, Quicki, and McAuley values, although they were not statistically significant. Waist circumference was significantly reduced from baseline after three months (-2.50±0.86 cm), as was the incidence of metabolic syndrome (19%). Follow up visits showed that these results were sustained one month after the end of the supplementation phase, but not further (Tsai *et al.* 2012).

Two studies examined effects of bitter gourd fruit pulp on diabetic patients with no adjunct therapy (Welihinda *et al.* 1986; Fuangchan *et al.* 2011). Wehlihinda *et al*. (1986) examined effects of a single dosage of 100 mL clear bitter gourd juice on type 2 diabetes patients. Participants received either bitter gourd or placebo 30 minutes before receiving a glucose load. The bitter gourd juice significantly improved glucose tolerance and revealed a significantly lower area under the curve than placebo (187.0 cm vs. 243.6 cm, respectively). This

study also showed that there were responders and nonresponders to bitter gourd treatment. In the study by Wehlihinda *et al*. (1986) 73% (n=13) responded to bitter gourd and 27% (n=5) did not. This response rate is higher than in the current setting, where around 60% responded to bitter gourd supplementation. In the current study, nonresponding may be due to a normal FPG level or genetic factors in participants. The current study also aimed to conduct single nucleotide polymorphism (SNP) analysis, in which genetic variations between responders and nonresponders are compared. However, the quality of DNA samples was insufficient for SNP analysis. A new collection of DNA samples of study participants, planned for 2016, may provide insights into differences between responders and nonresponders. The observation of nonresponders has also been reported in studies using oral hypoglycemic drugs (Groop *et al.* 1986; Khan *et al.* 2015).

Fuangchan *et al*. (2011) examined the effects of 500 mg, 1000 mg, and 2000 mg of bitter gourd fruit pulp, or 1000 mg of metformin, per day for four weeks on newly diagnosed type 2 diabetic patients in a placebo-controlled trial. There were no statistically significant effects of the 500 mg and 1000 mg dosages. Supplementation of 2000 mg bitter gourd significantly reduced fructosamine levels from a baseline of 18.14±2.93 mmol/L to 17.57±2.67 mmol/L. This glucose-lowering effect, however, was smaller than with metformin supplementation, during which fructosamine levels dropped significantly from 17.11±3.78 mmol/L to 16.18±2.89 mmol/L. In addition, metformin significantly reduced FPG and 2-h plasma glucose levels, whereas bitter gourd supplementation did not. Bitter gourd supplementation did not show any effect on these outcomes (Fuangchan *et al.* 2011).

Tsongia *et al*. (2004) studied the effect on type 2 diabetic participants of 200 mg methanolic bitter gourd extract taken twice per day (BD) and OAD taken for seven days. The study was divided into two stages and three groups. In the first weeklong stage, participants received either 0.5 g metformin BD, 5.0 g glibenclamide, or a combination of both (0.5 g metformin BD + 5.0 g glibenclamide BD). In the second weeklong stage, study groups received 200 mg bitter gourd extract BD and half the standard dosage of the metformin, glibenclamide, or combination. At the end of week two, bitter gourd supplementation corresponded to significantly lower fasting and postprandial glucose levels compared to only the drug treatment in week one. Specifically, bitter gourd increased the glucose-lowering effect of half the standard

metformin dosage on FPG and postprandial plasma glucose by 10% and 17%, respectively. Further, it enhanced the glucose-lowering effect of half the standard dosage of glibenclamide on these parameters by 11% and 15%, respectively. The authors assume a synergistic effect of OAD and chemical constituents of bitter gourd, such as alkaloids, sterols, glycosides, and tannins (Tongia *et al.* 2004).

Dans *et al*. (2007) examined effects of 3 g bitter gourd (*Charantia* Ampalaya Capsules©) taken for three months on newly or poorly controlled type 2 diabetic cases. The study group did not find any statistically significant differences between the bitter gourd and placebo groups with regard to FPG, HbA_{1c}, body weight, or total cholesterol (Dans *et al.* 2007).

Zänker *et al*. (2012) investigated effects of 1 g bitter gourd extract in capsule form (Glucokine®) taken for four months on type 2 diabetes mellitus participants (with or without concomitant oral hypoglycemic drug therapy). The study included three arms. In one arm, participants received 1 g of bitter gourd. In the second arm, participants received 1 g bitter gourd in combination with chromium and zinc supplementation capsules. In the third arm, participants received a placebo. There was no effect or treatment difference between groups with regard to FPG. However, there were statistically significant decreases in HbA_{1c} levels compared to baseline within the bitter-gourd-only group and the placebo group. The bitter gourd group showed a larger effect than the placebo group (6.47±0.63% to 6.28±0.57% vs. 6.51±0.65% to 6.41±0.76%) (Zänker *et al.* 2012).

Kochhar and Nagi (2011) examined the effects of a raw or cooked combination of bitter gourd, fenugreek seeds, and jambu seeds (all in equal amounts), on type 2 diabetic patients with or without OAD therapy. This study was divided into two phases. In the first phase, 1 g per day was given to diabetic patients in either raw (capsule) or cooked (biscuit) form for 45 days. In the second phase, the dosage was doubled for 45 days. After the first phase, there was a statistically significant drop in FPG and postprandial plasma glucose compared to baseline in both groups, with a larger effect in the group receiving the raw mixture. In this group, FPG levels dropped from 9.95±0.34 mmol/L to 7.85±0.28 mmol/L and postprandial plasma glucose levels dropped from 13.41±0.35 mmol/L to 9.73±0.31 mmol/l. In the other group, FPG levels dropped from 9.43±0.31 mmol/L to 7.90±0.35 mmol/L and postprandial plasma glucose levels dropped from 11.4±0.28 mmol/L to 9.83±0.27 mmol/L. After the second phase, both outcomes further

significantly decreased to 5.89±0.21 mmol/L and 7.52±0.19 in the first group and 6.55±0.30 mmol/L and 9.67±0.25 mmol/L in the second group, respectively. In addition, after phase two, glucose excretion was lower in fasting and postprandial urine samples compared to baseline. The study group also assessed effects of bitter gourd supplementation on the use of OAD and found a decrease in their usage from 88% at baseline to 33% at the end of phase two (Kochhar *et al.* 2011).

In the presented studies, bitter gourd supplementation did not always have hypoglycemic effects in diabetic patients. This may be due to different designs, dosages, durations, outcome measures, and statistical analyses, as well as the characteristics of the study subjects, which are summarized in Table 21. Unlike the current study, many of the others only included a small number of participants and were not placebo controlled. Another advantage of the current study was the cross-over design, which reduces the between-subject variability.

Table 21 Overview on human studies with bitter gourd among pre-diabetic or diabetic patients (adapted from (Habicht *et al.* 2014)

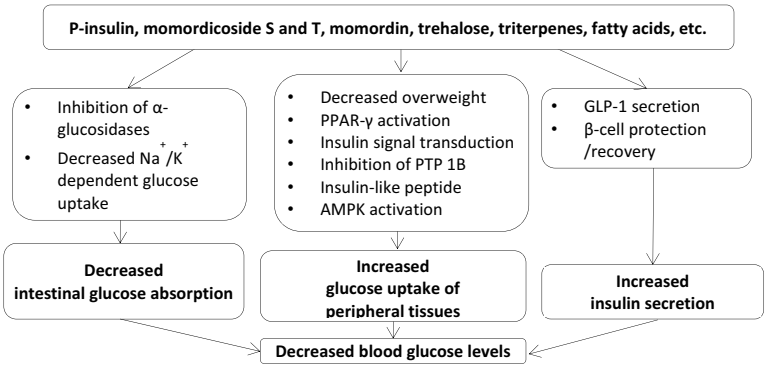
Study design [reference]	Study subjects	Dosage (all oral)	Duration	Preparation	Effects (p<0.05)
Randomized single-blind placebo-controlled cross-over	44 Pre-diabetics	2.5 g per day	8 weeks	Dried whole fruit powder mixed with 150 ml water	Glucose-lowering effect on fasting plasma glucose
Open-labeled single-arm study (Tsai *et al.* 2012)	42 patients diagnosed with metabolic syndrome	4.8 g per day	3 months	Whole fruit powder capsules	Decreased incidence rate of metabolic syndrome among study population; Lower waist circumference
Randomized single-blind placebo-controlled (John et al. 2003)	50 type 2 diabetic patients	6 g per day	4 weeks	Dried whole fruit powder pressed to tablets / riboflavin as placebo	No effect
Not placebo-controlled (Tongia *et al.* 2004)	15 type 2 diabetic patients	200 mg per day in addition to metformin, glibenclamide, or both	7 days	Methanolic fruit extract	Lower fasting and postprandial glucose levels compared to the drug treatment alone

Table 21 continued: Overview on human studies with bitter gourd among pre-diabetic or diabetic patients (adapted from (Habicht *et al.* 2014)

Study design [reference]	Study subjects	Dosage (all oral)	Duration	Preparation	Effects ($p<0.05$)
Randomized double-blind placebo-controlled (Dans *et al.* 2007)	40 newly diagnosed type 2 diabetic patients or patients with poor blood glucose control	3 g per day in addition to standard therapy	3 months	Charantia Ampalaya Capsules© and placebo	No effect
Not placebo-controlled (Srivastava *et al.* 1993)	Diabetic patients (7 patients tested extract / 5 patients tested tablets)	100 mL (extract) or three times a day 5 g (tablet)	7 weeks (extract) or 3 weeks (tablet)	Aqueous extract / fruit powder as tablet	Lower postprandial blood glucose and HbA1c levels after treatment with bitter gourd extract; No effect after treatment with bitter gourd tablets
Not placebo-controlled (Welihinda *et al.* 1986)	18 newly diagnosed type 2 diabetic patients without anti-diabetic drugs	100 mL	Single dosage	Clear juice from the flesh of Sri Lankan bitter gourd variety / distilled water as control	Improved glucose tolerance; Indication for possible non-responders
Randomized double-blind active-controlled, dosage was placebo-controlled (Fuangchan *et al.* 2011)	143 newly diagnosed type 2 diabetic patients	500 / 1000 / 2000 mg per day or 1000 mg metformin per day	4 weeks	Capsules of dried fruit pulp powder or metformin / roasted rice powder and lactose as placebo	Reduced fructosamine levels only with 2000 mg per day
Not placebo-controlled (Kochhar *et al.* 2011)	60 type 2 diabetic patients free from serious complications	45 days 1 g per day + 45 days 2 g per day	90 days	Mixed powder of bitter gourd fruit, fenugreek seeds, and jambu seeds in either raw (capsule) or cooked (biscuit) form	Lower fasting and postprandial glucose levels in blood and urine; Reduced intake of oral hypoglycemic drugs; Raw powder was more effective
Double-blind placebo-controlled (Zänker *et al.* 2012)	97 type 2 diabetic patients with or without oral anti-diabetic therapy	1 g per day	4 months	Water soluble bitter gourd extract (Glucokine®) with or without chromium and zinc supplementation in capsules	Decreased HbA1c after bitter gourd treatment without chromium and zinc supplementation

5.2.2 Mechanisms of glucose lowering effects of bitter gourd

The observed hypoglycemic effects in human studies are due to glucose-lowering components in bitter gourd. Many different compounds in bitter gourd have been investigated in cell and animal studies (Joseph *et al.* 2013; Singh *et al.* 2011; Habicht *et al.* 2014). Three major mechanisms, shown in Figure 23 are responsible for the glucose-lowering effect by decreasing intestinal glucose absorption, increasing insulin secretion, and increasing glucose uptake in peripheral tissues (Habicht *et al.* 2014), shown in Figure 23. Other examined mechanisms include an inhibition of adipocyte differentiation (Nerurkar *et al.* 2010) and a suppression of key gluconeogenic enzymes (Shibib *et al.* 1993; Singh *et al.* 2011), among others (Joseph *et al.* 2013). Some of the isolated compounds in bitter gourd responsible for hypoglycemic effects are p-insulin (polypeptide-p), momordicosides, oleanic acid, trehalose, and momordin. The p-insulin, revealed an insulin-like effect in type 1 and type 2 diabetic patients after subcutaneous administration (Khanna *et al.* 1981). In in-vitro, ex-vivo, and animal studies, momordicoside S and T showed increased glucose tolerance and improved insulin sensitivity (Tan *et al.* 2008). Oleanolic acid increased the release of intestinal glucagon-like-peptide-1 (GLP-1) (Huang *et al.* 2013), trehalose decreased postprandial blood glucose levels (Matsuur *et al.* 2002), and momordin activated peroxisome proliferator-activated receptor-γ (PPAR-γ) (Sasa *et al.* 2009).



PPAR: peroxisome proliferator-activated receptor, PTP 1B: protein tyrosine phosphatase 1B, AMPK: adenosine monophosphate-activated protein kinase, GLP-1: glucagon-like-peptide-1

Figure 23 Overview on hypoglycemic mechanisms of bitter gourd constituents, adapted from (Habicht *et al.* 2014)

5.2.3 Effects on body weight, blood pressure, and blood lipids

In the current study, there were no significant differences with regard to BMI, blood lipid parameters, and BP between bitter gourd and placebo groups. This was similar to the study by Dans et al. (Dans *et al.* 2007), where no effect was observed on total cholesterol and body weight. The absence of an effect on HDL, Chol, and TG in the current setting might be due to the fact that blood lipids of study participants were mostly within normal ranges.

In several animal studies (Table 22), bitter gourd treatment was shown to improve lipid profiles of diabetic and obese mice and rats (Ahmed *et al.* 2001; Chaturvedi *et al.* 2004; Nerurkar *et al.* 2008; Gadang *et al.* 2011).

Table 22 Effects of bitter gourd on lipids in diabetic and obese rats and mice (Alam *et al.* 2015)

Model [reference]	Dosage	Effects
STZ-induced diabetic rats (Ahmed et al. 2001)	10 mL 100% fruit extract per kg body weight per day for 10 weeks	Decreased elevated level of plasma cholesterol, triglycerides, and phospholipids
Diabetic rats (Chaturvedi *et al.* 2004)	140 mg per kg body weight for 30 days	Decreased triglycerides and low-density lipoprotein
Female C57BL/6 mice fed with HFD (Nerurkar *et al.* 2008)	1.5% freeze-dried bitter gourd juice with diet	Normalized triacylglycerol, cholesterol and NEFA; Normalized AST, ALT, and ALP in plasma; Decreased ApoB secretion and modulated phosphorylation status of insulin resistance and its downstream signaling molecules
Female Zucker rats (Gadang *et al.* 2011)	3.0% (wt=wt) bitter gourd seeds	Increased expression of PPAR-γ in the WAT; Decreased total cholesterol, and LDL cholesterol, and increased HDL cholesterol; Downregulated expression of PPAR-γ, nuclear factor-kB, and interferon-γ mRNA in heart tissue

NEFA: non-essential fatty acid, AST: Aspartate transaminase, ALT: alanine transaminase, ALP: Alkaline phosphatase, ApoB: apolipoprotein B, PPAR: peroxisome proliferator-activated receptor, -kB: kappa-light-chain-enhancer, mRNA: messenger ribonucleic acid

In the current study, participants were asked to not change their eating and physical activity habits during the study period, and therefore avoid significant changes in BMI due to dieting or

increased physical activity during bitter gourd consumption. In animal studies (Table 23), bitter gourd treatment showed a significant reduction in body weight gain in groups treated with bitter gourd compared to placebo (Chan *et al.* 2005; Huang *et al.* 2008; Klomann *et al.* 2010). Tsai at al. (Tsai *et al.* 2012) also found no effect on BP outcomes.

Table 23 Effects of bitter gourd on body weight, obesity, and adiponectin dysfunction, adapted from (Alam *et al.* 2015)

Model [reference]	Dosage	Effects
High-fat-diet-induced fat rats (Chan *et al.* 2005)	0.75% and 1.5% extracts	Decreased body weight, visceral fat mass, plasma glucose, and triacylglycerole Increased plasma catecholamines
Male C57BL/6J mice, 5 weeks old (Shih *et al.* 2008)	0.5 g/kg per day 1.0 g/kg per day P-fraction extract (whole fruit incl. pulp and seed) or 0.2 g/kg per day 1.0 g/kg per day G-fraction extract (whole fruit)	Decreased body weight and visceral fat Decreased plasma glucose, triglycerides, and total cholersterol Increased free fatty acid Increased mRNA expression of leptin, PPAR-γ, PPAR-α, and decreased expression of resistin
Male Wistar rats fed high-fat diet (Huang *et al.* 2008)	5% (w/w) powder	Decreased body weight and adipose tissues Decreased triacylglycerol and cholesterol Increased adiponectin
Overweight rats (Farhat Bano 2011)	Aqueous extract 2 mL per day	Reduced elevated body weight gain and cholesterol, triglycerides, and low-density lipoprotein cholesterol Increased high density lipoprotein cholesterol

PPAR: peroxisome proliferator-activated receptor, mRNA: messenger ribonucleic acid

5.2.4 Adverse events and side effects compared to other bitter-gourd studies and diabetic treatments

In the current study, adverse effects after bitter gourd consumption were gastric complaints, flatulence, loose stool, diarrhea, headache, nausea, and vomiting. No hypoglycemic events were reported. During the period 2, four female participants dropped out due to nausea and vomiting after consumption of bitter gourd. This might be linked to the slightly bitter taste of the fruit, despite the blinding, and a possible development of an aversion to it. The palatability of bitter gourd may be improved to avoid the bitter taste and related side effects. However, as bitter gourd was consumed after the main meal, it is difficult to identify a clear causal relationship between its consumption and side effects or adverse events. In addition, perceived side effects may be linked to concurrent diseases and intake of medications during the study period. The low dropout rate of 15% during the six-month study period demonstrates participants' interest in their health and well-being, as well as a tolerance for the study product.

The side effects reported in the current study were also reported in other studies. Within these studies, the most common adverse events reported were gastrointestinal complaints, headache, dizziness, and nausea. These adverse events did not differ compared to those for placebo or OAD (Tsai *et al.* 2012; Fuangchan *et al.* 2011; Dans *et al.* 2007).

In the current setting, there was no significant influence of bitter gourd supplementation on creatinine and GPT levels. This result is similar to observations in the other studies that aspartate aminotransferase or alanine aminotransferase were not altered by bitter gourd treatment (Fuangchan *et al.* 2011; Tsai *et al.* 2012; Dans *et al.* 2007; Zänker *et al.* 2012). Further, in other studies, no changes were seen in sodium and potassium levels (Dans *et al.* 2007; Tsai *et al.* 2012), alkaline phosphatase, or glutamyl transferase (Tsai *et al.* 2012; Zänker *et al.* 2012).

In the current trial and presented studies, bitter gourd as a medicinal plant seemed to be safe for consumption by study subjects. However, consumption of bitter gourd is not recommended for pregnant and lactating women, because animal studies have shown negative effects on fertility and because it has been used as an abortifacient agent (Grover *et al.* 2004; Raman, A. *et al.* 1996). Further, a glycol alkaloid known as vicine has been isolated from bitter gourd seeds (Haixia *et al.* 2004). Vicine, also found in fava beans, can cause hemolytic anemia after consumption by people with G6PD deficiency, so consumption by such people is not

recommended. However, so far, there have not been any reports of hemolytic anemia after bitter gourd consumption (Joseph *et al.* 2013).

5.2.5 Glucose lowering effect due to behavior change?

As reported in chapter 4.2.5, there was a significant decrease in FPG between screening and baseline_1. Figure 24 shows that all participants had a pre-diabetic FPG as required by inclusion criteria at screening, but that some had a normal FPG at baseline.

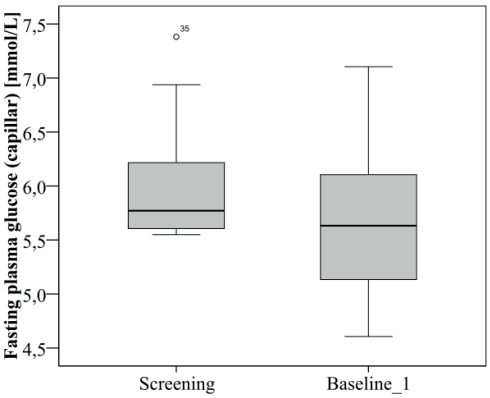


Figure 24 Boxplot of fasting plasma glucose of overall study group at screening and baseline_1

As shown in Table 24 p. 89, there were no significant differences in HbA_{1c} or BMI. However, there was a significant decrease in systolic BP. These effects may be due to behavioral changes. During the screening, counseling on a healthy lifestyle was provided to participants, if requested, and included recommendations to increase vegetable intake, moderate alcohol intake, and engage in physical activity. However, as no data were collected on whether participants changed their lifestyle after being identified as having pre-diabetic glucose level, no clear conclusions can be drawn. Nonetheless, lifestyle changes may be a feasible way to improve FPG among pre-diabetic people. A study on the effect of lifestyle interventions on glycemic status is needed in this study area to address the issue.

Table 24 Various variables of overall study group (n=52) at screening and baseline_1

Time point / Variable	Screening	Baseline_1	*p*
Fasting plasma glucose, mmol/L	5.97 ± 0.45	5.67 ± 0.61	0.001
HbA_{1c}, %	5.87 ± 0.41	5.84 ± 0.43	n.s.
Body mass index, kg/m²	29.8 ± 2.4	29.7 ± 2.3	n.s.
Systolic blood pressure, mmHg	127.8 ± 15.0	122.4 ± 15.8	0.001
Diastolic blood pressure, mmHg	85.5 ± 9.3	83.6 ± 10.8	n.s.

In other studies, lifestyle interventions were successful in reducing the diabetes incidence by 30%-60% among participants with IGT (Pan *et al.* 1997; Knowler *et al.* 2002; Chan *et al.* 2009; Tuomilehto *et al.* 2001). However, weight loss accompanied most of the interventions, unlike in the current setting. One study assessed sustainability of the intervention after 10 years and found no long-term effectiveness (Diabetes Prevention Program Research Group *et al.* 2009). No data are available for prevention programs including participants with IFG or pre-diabetic HbA_{1c} (Yudkin *et al.* 2014).

5.3 Framework of diabetes

The author of the current dissertation modified the conceptual framework model of malnutrition by UNICEF (1990) (Figure 25, p. 90). The framework model of malnutrition visualizes basic, underlying, and immediate causes of malnutrition, which lead to a manifestation of malnutrition. These causes are linked to various levels, ranging from the societal level (basic causes), to the household and community level (underlying causes) toward the individual level (immediate causes).

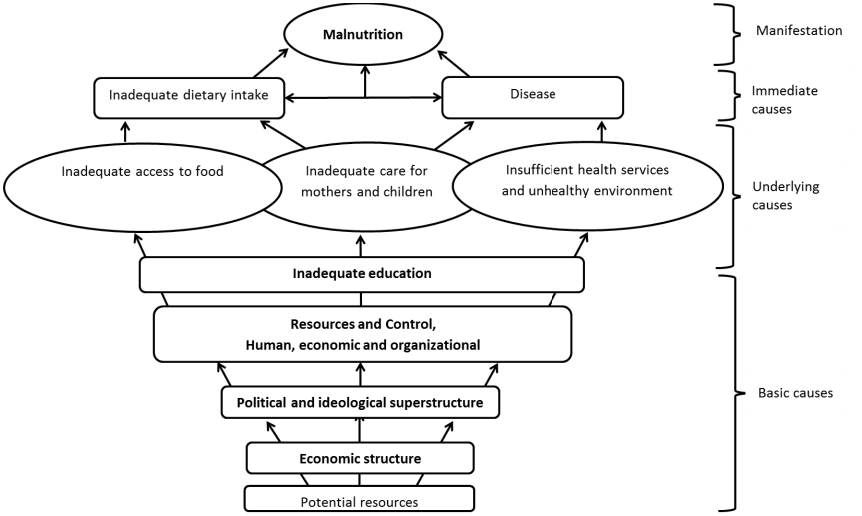


Figure 25 Conceptual framework of malnutrition (UNICEF 1990)

This model was adapted according to the results of the current and other studies, and observations of the study area to conceptualize causes, problems, and challenges linked to type 2 diabetes mellitus (Figure 26, p. 91). In the following, only findings related to the current research project are described. The research study among diabetic patients at KCMC identified a lack of sufficient health personnel, medical treatment, and diabetes knowledge among participants. Medical insurance that covered the costs for diabetes care was only available for 50% of interviewed patients. Thus, payment for diabetes treatment imposes a burden on diabetic patients and may influence outcomes of diabetes care. All these findings are examples of basic and underlying causes and challenges.

A study conducted in 2012 among urban residents of Moshi revealed food intakes high in refined carbohydrates and fatty foods, combined with a sedentary lifestyle (Ludwig *et al.* 2013). During the recruitment procedure for the dietary intervention study in 2013, high rates of pre-diabetes, undiagnosed diabetes, high glycemic levels among treated diabetes patients, obesity, and hypertension were detected. These findings are examples of the immediate challenges and causes of type 2 diabetes mellitus. To tackle the manifestation of type 2 diabetes

mellitus in this research area, multi-faced approaches with collaborations and efforts on the different levels along the conceptual framework are needed.

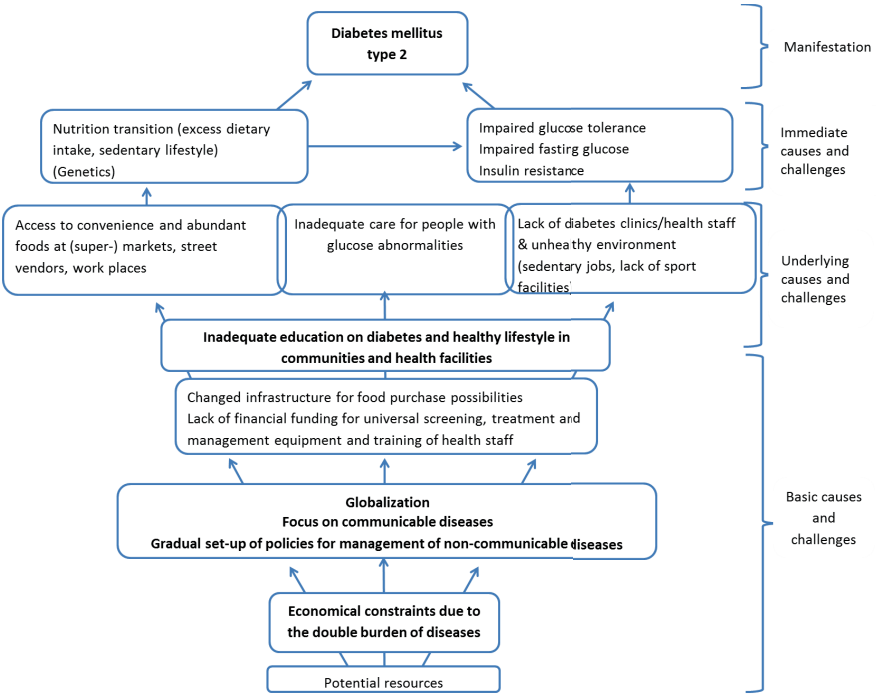


Figure 26 Conceptual framework of diabetes mellitus, adapted from (UNICEF 1990)

5.4 Limitations

The study population was selected for a dietary intervention study using a particular recruitment procedure, such that it was not representative of the project region or the whole of Tanzania. Because the screening was tailored to include overweight and obese people, conclusions cannot be drawn about the overall population. However, the results provide

insights into health-related issues that should be further assessed and addressed. Most measurements were only performed once, and there was no measurement of IGT to compare to FPG levels. The measurement of FPG was an easy and accepted method of assessing glycemic status in this setting. The point-of-care device used did not require electricity or extensive training of health staff. Zhao et al. demonstrated that the measurement of glycemic status using a capillary blood sample is a feasible screening method in a low-resource setting (Zhao *et al.* 2012). If FPG cannot be measured, RBG may be measured instead. Studies have demonstrated that a single RBG measurement of >100 mg/dL (Bowen *et al.* 2015) or >125 mg/dL (Ziemer *et al.* 2008) were good predictors of diabetes. As HbA_{1c} values had to be corrected afterwards, the results should be interpreted cautiously. During the pre-screening, BP was not assessed after five minutes rest, after which values might be lower. However, values were comparable to national data. This study was not designed as a screening for diabetes, but did detect high levels of undiagnosed diabetes. Further research is needed to analyze costs and benefits of screening activities in that region.

The current intervention study had several limitations. Not all participants were classified as IFG at their baseline assessment, which may have affected the glucose-lowering effect of bitter gourd. Although the study was a cross-over designed trial to reduce between-subject variability, the within-subject variability may have influenced the study outcomes. The detected period effect affected the statistical analyses and the sample size had to be recalculated. Although only 52 participants finished the study and only 44 venous blood samples were analyzed for the primary outcome, the final sample size achieved a power of 0.82 (according to a two-sample t-test) and statistical tests revealed a treatment difference despite the presence of a period effect. The food variety score calculated in the current study only includes information about food items consumed over the previous month, but not on the frequencies of consumption, which may have been modified. However, results of the regular checkup questionnaires showed that food intakes were mostly changed due to business trips or festivities. An influence of the medications taken by some participants prior to venous blood sampling on outcome parameters cannot be ruled out.

5.5 Conclusion and Outlook

The current study aimed to assess anti-diabetic effects of 2.5 g raw dry bitter gourd powder among pre-diabetic participants in Moshi, Tanzania. The recruitment procedure to identify pre-diabetic participants had an enrollment rate of 16% among people with a BMI of 27-35 kg/m² and an age of 30-65 years. The low concordance between FPG and HbA_{1c} values detected during screening needs further investigation, as well as the discrepancy between ADA and WHO definitions of IFG. Screening activities showed high rates of obesity, undiagnosed hypertension, and undiagnosed diabetes cases, which require further investigation and call for an establishment of health programs. Identified risk factors for increased FPG were age, WC, BMI, and having a family member with diabetes. The visited working areas and other settings were all receptive to health-related issues, which should be utilized for health promotion activities and education.

After the dietary intervention study, there was a significant treatment difference between the bitter gourd and placebo groups with a decrease of FPG in the bitter gourd and and increase in the placebo group. This treatment difference is based on the change of FPG between baseline and endline. The glucose lowering effect of bitter gourd was higher among participants who started with higher levels of baseline FPG. As the current study included pre-diabetic participants, the glucose-lowering effect of bitter gourd may be even more effective among diabetic participants. There were no further significant differences in other outcome variables between treatment groups.

In the overall study group, there was a significant reduction in FPG levels and systolic BP values between screening and baseline. This change might be due to a behavior change, as advice on a healthy lifestyle was provided during the screening, if requested by participants. The low dropout rate of 15% during the six-month study period underlines the interest in health and well-being. In conclusion, the consumption of 2.5 g dry bitter gourd (equivalent to 50 g fresh bitter gourd) in combination with education on a healthy lifestyle may be effective to lower raising blood glucose levels in the region and to prevent the progression of pre-diabetes to type 2 diabetes mellitus. However, bitter gourd consumption is not recommended for pregnant and lactating women as well as people with G6PD deficiency.

Summary

Prevalence of pre-diabetes and type 2 diabetes mellitus are on the rise not only in high-income countries, but also in low- and middle-income countries such as the United Republic of Tanzania, whereas many diabetes cases remain undiagnosed. Type 2 diabetes is often linked to overweight and obesity due to excess caloric intakes and sedentary lifestyles. In Tanzania, the most recent estimated prevalence of pre-diabetes was 9.1% (in 2013) and of diabetes 3.5% (in 2015). Access to proper diabetes care and management is often insufficient in Tanzania. The increasing rates of diabetes will amplify the already existent burden on affected individuals and the country on its own. Alternative strategies such as the use of anti-diabetic plants, may be one possibility to fight against rising blood glucose levels and prevent the onset of type 2 diabetes mellitus. One medicinal plant with hypoglycemic effects is *Momordica charantia*, also known as bitter gourd or bitter melon. Bitter gourd has shown anti-diabetic effects in cell, animal, and human studies, but no clear recommendation on the application of bitter gourd variety, dosage, and mean of consumption is available. Bitter gourd is most commonly cultivated and consumed in Asian countries. Bitter gourd is also available in Sub-Saharan countries, mainly collected from the wild. The current research project was divided into two studies which were conducted in Moshi, Tanzania, between 2011-2014. The first study aimed to assess knowledge and usage of bitter gourd as well as knowledge and management of diabetes among diabetic patients. The second study aimed to assess anti-diabetic effects of 2.5 g dry raw bitter gourd powder consumption per day among pre-diabetics.

The first study was a cross-sectional survey with structured and open-ended questions and conducted at the Kilimanjaro Christian Medical Centre in Moshi, in 2011. Out of 155 patients interviewed, 7% had heard about bitter gourd before, whereas 5% used it as a medicinal plant in adjunct to oral anti-diabetic drugs (OAD). Although bitter gourd was not well known, bitter tasting plants were consumed by almost all participants and around 50% stated to apply medicinal plants for various conditions. Symptoms were perceived between months and years before diagnosis. In regard to diabetes knowledge, symptoms were most known among patients followed by complications and causes. Almost all were on medical treatment, either on OAD, or insulin, or a combinations of both. Complications such as impaired sight and impotence

were stated by the patients. Around 90% stated to have changed their lifestyle after diagnosis toward higher intakes of vegetables and increased physical activity.

The second study was a cross-over designed, randomized, placebo-controlled, single-blind, dietary intervention trial among pre-diabetic participants in 2013/14. It was conducted at the Kilimanjaro Clinical Research Institute in Moshi and included two eight-week intervention periods, separated by a four week washout period. Fasting plasma glucose (FPG), HbA_{1c}, blood pressure (BP), and blood lipids were main assessed outcomes. Participants were recruited with the help of a pre-screening and screening phase in 2013. The following main inclusion criteria were applied: FPG 5.6-7 mmol/L, HbA_{1c} 5.7-7.5%, BMI 27-35 kg/m², BP 90/60-160/110 mmHg, age 30-65 years, no clinically diagnosed diseases, no pregnancy or breastfeeding among women.

A total of 1256 people were pre-screened, and 382 who fit age and BMI criteria were further screened. Around 35% of screened people had pre-diabetic FPG values. After assessing all inclusion criteria, 61 participants (54% female, 46% male) started the intervention study. After the study duration of six months, the dropout rate was 15% with 52 participants finishing the study. Statistical analysis with a general linear mixed model revealed a period, but no carry-over effect. The change of FPG levels significantly differed (p=0.01) between the bitter gourd and placebo groups, with a mean decrease in the bitter gourd (-0.2 mmol/L) and mean increase in the placebo group (0.1 mmol/L). Change of FPG was greater among participants with a higher baseline FPG. Other outcomes did not differ significantly. However, in the overall study group, there was a significant decrease of FPG and BP from the time of the screening (July-October 2013) until the start of the intervention study (October 2013).

In conclusion, the first study showed a positive attitude toward the use of medicinal plants. However, in case of bitter gourd, usage and knowledge were very low. As symptoms of diabetes were present a relatively long time before diagnosis, diabetes knowledge of diabetic patients was presumably gained after diagnosis with the help of health staff and information posters displayed in the clinic. In addition, diabetes care imposed extra burdens on some participants. The existence of complications shows the need to improve diabetes management, including possibilities to monitor long-term glucose levels.

The recruitment procedure of the second study revealed high rates of diagnosed and undiagnosed diabetes. The intervention study demonstrated a blood glucose lowering effect of

daily bitter gourd consumption among pre-diabetics. The change of FPG prior to the study may be attributable to a behavior change after the screening. A combination of healthy lifestyle counseling and use of bitter gourd (with exception for pregnant or lactating women, and people with glucose-6-phosphatase-dehydrogenase deficiency) may be a feasible strategy to reduce blood glucose levels in that area.

Zusammenfassung

Die Prävalenz von Prädiabtetes und Typ 2 Diabetes mellitus steigt nicht nur in einkommensstarken, sondern auch in niedrig- und mitteleinkommensstarken Ländern, wie Tansania. Dabei sind viele der Diabetesfälle noch nicht diagnostiziert. Typ 2 Diabetes wird häufig in einen Zusammenhang mit Übergewicht und Adipositas gebracht, welches durch eine überschüssige Kalorieneinnahme und einen bewegungsarmen Lebensstil bedingt sein kann. Die neueste geschätzte Diabetesprävalenz Tansanias aus dem Jahr 2015 lag bei 3,5% und die neueste geschätzte Prädiabetesprävalenz aus dem Jahr 2013 bei 9,1%. In Tansania ist der Zugang zur Fürsorge und Behandlung von Diabetes unzureichend. Zunehmende Prävalenzen an Prädiabetes und Diabetes verstärken die schon bestehende Belastung Betroffener und des Landes in Bezug auf die Bekämpfung der Erkrankung. Alternative Strategien, wie die Anwendung anti-diabetischer Pflanzen, könnte einen Ansatz darstellen, um präventiv steigenden Blutglucosewerten und den Ausbruch von Diabetes entgegen zu wirken. Eine solche Pflanze mit anti-diabetischen Wirkungen stellt *Momordica charantia* dar. Sie ist u.a. auch als Bittergurke oder Bittermelone bekannt. Die hypoglykämischen Wirkungen der Bittergurke wurden in vielen Zell-, Tier- und Humanstudien gezeigt. Bis heuten liegen aber noch keine genauen Empfehlungen über die Nutzung der Bittergurke und Dosierung dieser zur Blutzuckerkontrolle vor. Bittergurke wird vor allem in asiatischen Ländern kultiviert und verzehrt. In Ländern Subsahara Afrikas wird Bittergurke häufig als Wildpflanze gesammelt und konsumiert. Das vorliegende Forschungsprojekt war in zwei Studien gegliedert und wurde in Moshi Tansania durchgeführt. Die erste Studie zielte darauf ab, das Wissen und den Gebrauch der Bittergurke sowie das Wissen über und die Behandlung von Diabetes bei Diabetespatienten zu untersuchen. Das Ziel der zweiten Studie war, die anti-diabetische Wirkungen von 2,5 g roher getrockneter und pulverisierter Bittergurke unter Prädiabetikern zu untersuchen.

Die erste Studies stellte eine Querschnittserhebung mit standardisierten Fragebögen (strukturierte und offene Fragegestellungen) dar und wurde 2011 am Kilimanjaro Christian Medical Centre in Moshi durchgeführt. Von den 155 befragten Patienten, kannten 7% die Bittergurke und 5% nutzten diese bereits als medizinisches Mittel zusätzlich zu ihrer normalen Medikation. Obwohl wenige der Befragten die Bittergurke kannten, verzehrten fast alle

Studienteilnehmer bitter schmeckende Pflanzen und ca. 50% der Befragten wandten bereits Phytomedizin an. Bei vielen zeigten sich Symptome Monate und Jahre vor der Bekanntgabe der Diagnose. In Bezug auf das Wissen über Diabetes stellte sich heraus, dass die Befragten ein höheres Wissen über Symptome der Diabeteserkrankung hatten als über Komplikationen und Ursachen von Diabetes. Fast alle der Patienten waren unter medikamentöser Behandlung, entweder mit oralen anti-diabetischen Medikamenten, Insulin oder einer Kombination aus beiden. Genannte Komplikationen der Patienten waren verminderte Sehstärke, Impotenz und Bluthochdruck. Ungefähr 90% der Befragten gaben an, dass sie nach der Feststellung der Diagnose ihren Lebensstil hin zu höherem Gemüsekonsum und gesteigerter körperlicher Aktivität geändert hatten.

Die zweite Studie war eine cross-over, randomisierte, placebokontrollierte, einzeln verblindete, Ernährungsinterventionsstudie unter Prädiabetikern in 2013/14. Die Studie fand am Kilimanjaro Clinical Research Institute in Moshi, Tansania, statt und gliederte sich in zwei Interventionsphasen bestehend aus je acht Wochen. Die zwei Interventionsphasen waren durch eine vierwöchige Auswaschphase voneinander getrennt. Untersuchte Hauptuntersuchungs-parameter waren Nüchternblutglucose (NBG), glycolisiertes Hämoglobin (HbA_{1c}), Blutdruck und Blutlipide. Der Studie entsprechende Probanden wurden mit Hilfe eines zweistufigen Screenings im Jahr 2013 rekrutiert. Haupteinschlusskriterien waren: ein NBG von 5,6-6,9 mmol/L, ein HbA_{1c} von 5,7-7,5%, ein BMI von 27-35 kg/m², ein Blutdruck von 90/60-160/110 mmHg, ein Alter von 30-65 Jahren, keine klinisch diagnostizierte Erkrankung und keine vorliegende Schwangerschaft oder Stillzeit bei Frauen.

Insgesamt wurden 1256 Personen auf ihren passenden BMI und ihr passendes Alter untersucht. Von diesen hatten wiederum 382 der Studie entsprechende BMI- und Alterswerte und wurden auf die verbleibenden Einschlusskriterien überprüft. Ca. 35% der untersuchten Probanden wiesen eine prädiabetische NBG auf. Nach Überprüfung der verbleidenden Kriterien, wurden 61 Probanden, davon 54% weiblich, in die Studie aufgenommen. Nach sechsmonatiger Studiendauer lag die Dropoutrate bei 15% und somit beendeten 52 Probanden die Studie. Die statistische Analyse mittels eines allgemeinen linearen Modells zeigte einen Periodeneffekt, aber keinen carry-over Effekt. Die Veränderung des NBG war signifikant unterschiedlich (p=0,01)

zwischen der Bittergurken- und der Placebogruppe mit einem mittleren Abfall der NBG in der Bittergurkengruppe (-0,21 mmol/L) und einem mittleren Anstieg in der Placebogruppe (0,10 mmol/L). Eine höhere Senkung der NBG war bei Probanden, die mit einer höheren NBG die Studie begonnen hatten, zu erkennen. Die anderen Parameter unterschieden sich nicht signifikant zwischen den Behandlungsgruppen. Im Hinblick auf das gesamte Studienkolletiv der 52 Probanden zeigte sich bereits nach dem Zeitpunkt des Screenings während der Rekrutierungsphase (Juli bis Oktober 2013) und dem Beginn der Studie (Oktober 2013) ein signifikanter Abfall der NBG und des Blutdruckes.

Schlussfolgernd zeigte die erste Studie eine positive Einstellung der Studienteilnehmer gegenüber der Nutzung von Phytomedizin, auch wenn das Wissen und der Gebrauch der Bittergurke gering waren. Da Symptome bereits eine längere Zeit vor der Feststellung der Diagnose bei den Patienten vorhanden waren, ist das Wissen über eine Diabeteserkrankung vermutlich erst nach der Diagnose mittels Informationsposter in den Untersuchungsräumen erworben worden. Die Behandlung von Diabetes und damit verbundenen Kosten stellte für einige der Patienten eine zusätzliche Belastung dar. Diese Ergebnisse und das Vorhandensein von Komplikationen des Diabetes zeigen auf, dass es einen Bedarf gibt, Fürsorge und Behandlung von Diabetes zu verbessern.

Die zweite Studie wies einen Glucose-senkenden Effekt der Bittergurke bei täglicher Einnahme unter Prädiabetikern auf. Die Reduzierung der NBG vor der Studie ist womöglich auf einen Lebensstilwandel zurückzuführen, da die Probanden auf Nachfrage hin, Informationen bezügliche eines gesunden Lebensstiles erhalten hatten. Eine Kombination aus Bildung über einen gesunden Lebensstil und der Nutzung der Bittergurke könnte eine realisierbare Strategie darstellen, um steigende Blutglucosewerte in dieser Region Tansanias zu bekämpfen. Eine Einnahme der Bittergurke sollte allerdings nicht bei Schwangeren, Stillenden oder Personen mit einer Glucose-6-Phosphatdehydrogenase-Mangel empfohlen werden.

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Appendix

MOCHI, OUTPUT ONE | PATIENT'S QUESTIONNAIRE: PART 3: SOCIO-ECONOMICS | JUNE 2011 .

No: .....

1. Family name .....
Given name (s) .....
Gender ..... Male ☐ Female ☐
Age .....

2. Anthropometric data
Body weight (kg) ..... BMI .....
Body height (cm)

3. How many people belong to your household?
Children <5 years .....
Children 5-14 years .....
Female adults .....
Male adults .....

4. What is your marital status?
Single ☐
Married ☐
Separated/divorced ☐
Widowed ☐

5. What is your main occupation?
Farmer ☐
Farm labour service ☐
Non-farm casual service ☐
Business sector ☐
Artisan ☐
Carpenter ☐
Housewife ☐
Student ☐
Other, please specify ☐
.....

6. What is your highest level of education?
No formal education ☐
Few years primary ☐
Completed primary ☐
Few years secondary ☐
Completed secondary ☐
College ☐
Other, please specify ☐
.....

7. Which religion do you belong to?
Christianity ☐
Islam ☐
Hinduism ☐
Traditionalist ☐
Other, please specify ☐
.....

8. To which community do you belong to?
African community ☐
Asian community ☐
European community ☐
Other, please specify ☐
.....

9. What is the income level of your family?
High income ☐
Middle income ☐
Low income ☐
Below poverty line ☐

10. Do you own any of the following ...

10.1 ...items?
Radio ☐
Bicycle ☐
Motor cycle ☐
Car ☐
Mobile phone ☐
Electricity ☐
Iron roof ☐
Brick/cement wall ☐
Grass roof ☐

10.2 ...animals? **If yes, how many?**
Chicken ☐ .....
Goat ☐ .....
Sheep ☐ .....
Cow ☐ .....
Donkey ☐ .....
Goose/Duck ☐ .....
Others ☐ .....

10.3 ...sanitation & kitchen items?
Running water ☐
Flushing toilet ☐
Latrine ☐
Electricity ☐
Gas burner ☐
Cooking pot (metal) ☐
Earthenware ☐

11. Who is responsible for buying vegetables in your household?
Myself ☐
My spouse ☐
My housekeeper ☐
Other, please specify ☐
.....

12. Where do you buy vegetables?
Market ☐
Super market ☐
Other, please specify ☐
.....

13. Who is responsible for cooking in your household?
Myself ☐
My spouse ☐
My housekeeper ☐
grandmother ☐
Other, please specify ☐ .....

MOCHI, OUTPUT ONE | PATIENT'S QUESTIONNAIRE: PART 2: BITTER GOURD | JUNE 2011 No:.....

1.	**Have you ever heard about bitter gourd?** If no in question 1, continue with question 3	Yes ☐ No ☐
1.1	If yes, where did you hear about bitter gourd?	Market ☐ Radio and media ☐ Neighbors or friends ☐ Family members ☐ Doctor/Nurse ☐ Traditional healer / Herbalist Others, please specify ☐
1.2	If you have heard about bitter gourd, do you use bitter gourd to treat any disease(s)?	Yes ☐ No ☐
1.2.1	If yes, which disease(s)?	
1.2.2	If yes, how do you use it? (please describe preparation, amount & frequency	
1.3	If you have heard about bitter gourd did you hear anything about the use of bitter gourd to treat..	
1.3.1	...diabetes?	Yes ☐ No ☐
1.3.2	...overweight?	Yes ☐ No ☐
1.3.3	...hypertension?	Yes ☐ No ☐
1.3.4	...other diseases? If yes, please specify	Yes ☐ No ☐
2.	**Do you eat / drink any bitter gourd as a usual vegetable?** If no, continue with question 3	Yes ☐ No ☐
2.1	Is the bitter gourd available throughout the year?	Yes ☐ No ☐
2.2	If no, during which season is bitter gourd available	Dry season (Nov-Feb) Heavy rain season (March-June) Light rain season (July-Oct)
2.3	If you eat bitter gourd, how often do you eat bitter gourd?	Daily ☐ Several times a week ☐ Once a week ☐ Once a month ☐ Other, please specify ☐
2.4	If you eat bitter gourd, how do you eat / drink the bitter gourd?	Raw (e.g. as a salad) ☐ As a tea ☐ As a juice ☐ Boiled ☐ Fried ☐ Cooked with other vegetables ☐ Other, please specify ☐
2.5	If you eat bitter gourd, where do you usually get the bitter gourd from?	Market ☐ Super market ☐ Own garden ☐ Neighbors or friends ☐ Other, please specify ☐
3.	**Do you eat / drink any other bitter vegetables?**	Yes ☐ No ☐ I don't know ☐
3.1	If yes, what other bitter vegetables do you eat / drink	
3.2	If yes, how do you eat / drink the bitter vegetables?	Raw (e.g. as a salad) ☐ As a tea ☐ As a juice ☐ Boiled ☐ Fried ☐ Cooked with other vegetables ☐ Other, please specify ☐
4.	**Do you know any plant(s) that have good effects on diabetes or other disease(s)?**	Yes ☐ No ☐
4.1	If yes, can you name the plant(s)?	
4.2	If yes, can you name the disease(s) treated with these plant(s)?	
4.3	Do you eat any vegetables or other to treat diabetes or other diseases or medical conditions?	Yes ☐ No ☐
4.3.1	If yes, which vegetables or other plants do you eat for which diseases or medical condition?	
5.	**If you knew that eating specific vegetables would help you with your diabetes, would you...**	
5.1	eat these more often?	Yes ☐ No ☐ I don't know ☐
5.2	grow some in your own garden?	Yes ☐ No ☐ I don't know ☐
5.3	buy them?	Yes ☐ No ☐ I don't know ☐

MOCHI, OUTPUT ONE

PATIENT'S QUESTIONNAIRE: PART 1: DIABETES

JUNE 2011

No: .....

1. Which type of diabetes do you have? Type I ☐ Type II ☐ I don't know ☐

2 In what year were you diagnosed with diabetes? _____

2.1 Do you know any symptoms related to diabetes? Yes ☐ No ☐ I don't know ☐

2.2 If yes in question 2.1, which? _____

2.3 Which of the following symptoms did you notice before you were diagnosed with diabetes? (more than one answer is possible)

- Frequent trips to the bathroom ☐
- Unquenchable thirst ☐
- Weakness and fatigue ☐
- Tingling or numbness in your hands, legs or feet ☐
- Other, please specify _____ ☐

2.4 If yes, when did these symptoms start?

- Six months before diagnosis ☐
- One year before diagnosis ☐
- Two years before diagnosis ☐
- Other, please specify _____ ☐

2.5 Do you think that your diabetes is always well controlled? Yes ☐ No ☐ I don't know ☐

3. Do you know any complications of diabetes? Yes ☐ No ☐ I don't know ☐

3.1 If yes, what complications do you know? _____

3.2 If yes, do you have any of these complications? Yes ☐ No ☐ I don't know ☐

3.3 If yes in 3.2, please specify _____

3.4 Do you have any other medical conditions? Yes ☐ No ☐ I don't know ☐

3.5 If yes, what conditions do you have? _____

4. Do you take any medicine for your diabetes? Yes ☐ No ☐

4.1 If yes, what kind of medicine do you take? _____

4.2 If possible, would you specify the amount of your weekly expenses for your.

4.2.1 ...diabetes medication? _____

4.2.2 ...doctoral visits? _____

4.3 How often do you see the doctor to check for your diabetes?

- Weekly [ ]
- Monthly [ ]
- every two months [ ]
- Three to five times a year [ ]
- Once a year [ ]
- Less than once a year [ ]

4.4 Do you have to give up anything so you can pay for your medications? Yes ☐ No ☐

4.5 If yes, what items do you have to give up? _____

5 Do you have any family members who suffer from diabetes? Yes ☐ No ☐ I don't know ☐

5.1 If yes, who? (more than one answer is possible)

Father Mother
Brother Sister
Grandfather Grandmother
If other, please specify _____

5.2 Do you have family members who are overweight? Yes ☐ No ☐

5.3 If yes in 5.2, do you think, they would participate in an intervention study for diabetes prevention? Yes ☐ No ☐ I don't know ☐

6. Are you a member of a diabetes support group? Yes ☐ No ☐

6.1 If yes, what do you talk about in that group? _____

7. Do you know the causes of diabetes? Yes ☐ No ☐

7.1 If yes, what are the causes? _____

8. Do you think that your eating habits can affect your blood glucose level? Yes ☐ No ☐ I don't know ☐

8.1 Have you changed your eating habits since you were diagnosed with diabetes? Yes ☐ No ☐

8.2 If yes, what changes did you make? _____

8.3 Do you think that your physical activity can affect your blood glucose level? Yes ☐ No ☐ I don't know ☐

8.4 Have you changed your physical activity level since you were diagnosed with diabetes? Yes ☐ No ☐

8.5 If yes, what changes did you make? _____

Table D: Major recommendations on nutrition for diabetic patients (Franz *et al.* 2002)

Carbohydrates	**Grading**
Foods containing carbohydrate from whole grains, fruits, vegetables, and low-fat milk are important components and should be included in a healthy diet.	A
With regard to the glycemic effects of carbohydrates, the total amount of carbohydrate in meals or snacks is more important than the source or type.	A
Because sucrose does not increase glycemia to a greater extent than isocaloric amounts of starch, sucrose and sucrose-containing foods do not need to be restricted by people with diabetes, however, they should be substituted for other carbohydrate sources or, if added, be covered with insulin or other glucose-lowering medication.	A
Nonnutritive sweeteners are safe when consumed within the ADI levels established by the FDA.	A
Individuals receiving intensive insulin therapy should adjust their premeal insulin dosages based on the carbohydrate content of meals.	B
Although the use of low–glycemic index foods may reduce postprandial hyperglycemic, there is not sufficient evidence of long-term benefit to recommend use of low-glycemic index diets as a primary strategy in food/meal planning.	B
As far the general public, consumption of dietary fiber is to be encouraged; however, there is no reason to recommend that people with diabetes consume a greater amount of fiber than other Americans.	B
Individuals receiving fixed daily insulin dosages should try to be consistent in day-to-day carbohydrate intake.	C
Carbohydrate and monounsaturated fat should together provide 60–70% of energy intake. However, the individual's metabolic profile and need for weight loss should be considered when determining the monounsaturated fat content of the diet.	E

Table D continued: Major recommendations on nutrition for diabetic patients (Franz *et al.* 2002)

Protein	**Grading**
In individuals with controlled type 2 diabetes, ingested protein does not increase plasma glucose concentrations, although ingested protein is just as potent a stimulant of insulin secretion as carbohydrate.	B
For persons with diabetes, especially those not with less-than-optimal glucose control, the protein requirements may be greater than the RDA, but not greater than usual intake.	B
For individuals with diabetes, there is no evidence to suggest that usual protein intake (15–20% of total daily energy) should be modified if renal function is normal.	E
The long-term effects of diets high in protein and low in carbohydrate are unknown. Although such diets may produce short-term weight loss and improved glycemia, it has not been established that weight loss is maintained long-term. The long-term effect of such diets on LDL cholesterol is also a concern.	E
Fat	
In all, <10% of energy intake should be derived from saturated fats. Some individuals (i.e., those with LDL cholesterol ≥100 mg/dl) may benefit from lowering saturated fat intake to <70% of energy intake.	A
Dietary cholesterol intake should be <300 mg/day. Some individuals (i.e., those with LDL cholesterol ≥100 mg/dl) may benefit from lowering dietary cholesterol to <200 mg per day.	A
To lower LDL cholesterol, energy derived from saturated fat can be reduced if weight loss is desirable or replaced with either carbohydrate or monounsaturated fat if weight loss is not a goal.	B
Intake of transunsaturated fatty acids should be minimized.	B
Reduced-fat diets when maintained long term contribute to modest loss of weight and improvement in dyslipidemia.	B
Polyunsaturated fat intake should be ~10% of energy intake	C

Table D continued: Major recommendations on nutrition for diabetic patients (Franz *et al.* 2002)

Energy balance and obesity	**Grading**
In insulin-resistant individuals, reduced energy intake and modest weight loss improve insulin resistance and glycemia in the short-term.	A
Structured programs that emphasize lifestyle changes including education, reduced fat (<30% of daily energy) and energy intake, regular physical activity, and regular participant contact, can produce long-term weight loss on the order of 5 to 7% of starting weight.	A
Exercise and behavior modification are most useful as adjuncts to other weight-loss strategies. Exercise is helpful in maintenance of weight loss.	A
Standard weight-reduction diets, when used alone, are unlikely to produce long-term weight loss. Structured, intensive lifestyle programs are necessary.	A
Micronutrients	
There is no clear evidence of benefit from vitamin or mineral supplementation in people with diabetes who do not have underlying deficiencies. Exceptions include folate for prevention of birth defects and calcium for prevention of bone disease.	B
Routine supplementation of the diet with antioxidants is not advised because of uncertainties related to long-term efficacy and safety.	B
Alcohol	
If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two drinks for adult men. One drink is defined as a 12-oz beer, a 5-oz glass of wine, or 1.5-oz glass of distilled spirits.	B
To reduce risk of hypoglycemia, alcohol should be consumed with food.	B

Scientific principles ranked based on the American Diabetes Association grading system. The highest ranking, A, is assigned when there is supportive evidence from multiple, well-conducted studies; B is an intermediate rating; C is a lower ranking; and E represents recommendations based on expert consensus.

Screening Questionnaire Participant ID:..... Date.....Interviewer.....

1.	**Family name**		4 SMOKE	**Do you smoke or have you ever smoked?**	yes 1☐ no 2☐
	Given name (s)		4.1 SMOKA	**At what age did you start smoking, when did you stop?**	
VIL	**Village**		4.2 SMOKQ	**How many cigarettes are you smoking or where you smoking per day?**	
	Kitongoji (Area)				
	Balozi (village leader)		5 ALC	**Do you drink alcohol beverages?**	yes 1☐ no 2☐
	Tel.No.		5.1 ALCK	**If yes, what kind of alcohol?**	
AGE	**Age**		5.2 ALCA	**Which amounts?**	
GEND	**Gender**	**Male** ☐ **Female** ☐			
2 WORK	**What is your main occupation?**	1☐ Farmer 2☐ Farm labour service 3☐ Cattle pasteurist 4☐ Non-farm casual service 5☐ Business sector 6☐ Teacher 7☐ Artisan 8☐ Carpenter 9☐ Housewife 10☐ Student 88☐ Other, please specify	6 DISF	**Do you have any family members suffering from one of the following diseases?**	☐ Diabetes ☐ High blood pressure ☐ Obesity ☐ Heart problems
			7 DISD	**Do you have any diagnosed disease?**	yes 1☐ no 2☐
			7.1 DISK	**If yes, what kind of disease(s) do you have?**	
			8 MEDR	**Do you take any medication regularly?**	yes 1☐ no 2☐
			8.1 MEDK	**If yes, what kind of medication do you take?**	
3 EDUC	**What is your highest level of education?**	1☐ No formal education 2☐ Few years primary 3☐ Completed primary 4☐ Few years secondary 5☐ Completed secondary 6☐ College 88☐ Other, please specify	9 PREGC	**Are you currently pregnant**	yes 1☐ no 2☐
			9.1 PREGP	**Do you plan to get pregnant within the next year?**	yes 1☐ no 2☐
			9.2 BFEED	**Are you currently breast-feeding?**	yes 1☐ no 2☐

Socio-Economic and Health Questionnaire Participant ID. ..... Date.....Interviewer.....

1.	Family name: ----------		
	Given name: ----------		
	Address ----------		
	----------		
2. HHS	How many people belong to your household ----------		
3. MARST	What is your marital status	1 ☐	Single
		2 ☐	Married
		3 ☐	Divorced
		4 ☐	Widowed
4. TRAW	How to you get to work?	1 ☐	Walking
		2 ☐	Bicylce
		3 ☐	Bus
		4 ☐	TukTuk
		5 ☐	Motorbiketaxi
		6 ☐	Care
5. REL	What religion do you belong to?	1 ☐	Christian
		2 ☐	Islam
		3 ☐	Hinduism
		4 ☐	Traditional beliefs
		88 ☐	Other beliefs, please specify
6. COM	Which community do you belong to?	1 ☐	African community
		2 ☐	Asian communty
		3 ☐	European/American community
		88 ☐	Other

7. FOODR	Who is responsible for buying foods in your household?	1 ☐	Myself
		2 ☐	My spouse
		3 ☐	Housemaid
		88 ☐	Other
			----------
8. FOODW	Where do you buy your food?	1 ☐	Local market
		2 ☐	Supermarket
		88 ☐	Others
			----------
9. COOK	Who is responsible for cooking in your household?	1 ☐	Myself
		2 ☐	My spouse
		3 ☐	Housemaid
		4 ☐	Grandmother
		88 ☐	Other
			----------
10. SUPPL	Do you take any vitamin and mineral supplements?	1 ☐	Yes
		2 ☐	No
		99 ☐	I don't know
11. SUPPK	If yes, what kind of supplements		----------

Regular Check-Up Questionnaire Participant ID:.....Time:..... Date.....Interviewer....

1. Compl	Did you feel any complications after drinking the juice during last week?	1 ☐ Yes 2 ☐ No
1.1 Kcompl	If yes, what complication did you feel?	----------
2. EventH	Did you have any of the following events last week? Headache	1 Yes ☐ 2 No ☐
EventS	Stomach ache	☐ ☐
EventG	Gastrointestinal complaints	☐ ☐
EventD	Diahrrea	☐ ☐
EventF	Flatulence	☐ ☐
EventN	Nausea	☐ ☐
EventV	Vomiting	☐ ☐
EventF	Fever	☐ ☐
3. Mal	Did you have malaria last week?	1 ☐ Yes 2 ☐ No
3.1 MalMed	If yes, did you take any medication?	1 ☐ Yes 2 ☐ No
3.2 MalMedK	If yes, what medication did you take?	----------
4. Med	Did you take any other medication last week, e.g. against headache?	1 ☐ Yes 2 ☐ No
4.1 Medfor	If yes, what did you take the medication for?	----------
4.2 MedK	If yes, what kinda of medication did you take?	----------
5. Juice	How did you like drinking the juice last week?	 ☐ ☐ ☐ ☐ ☐
6. Bitter	How did you find the taste of the juice last week?	 ☐ ☐ ☐ ☐
7. Ehabi	Did you change your eating habits last week?	1 ☐ Yes ☐ No
7.1. ECHabi	If yes, what did you change?	---------- ----------
8. Ahabit	Did you change your level physical activity last week?	1 ☐ Yes ☐ No
8.1 ACHabi	If yes, what did you change?	---------- ----------
9.	Did you drink your juice every day last week?	1 ☐ Yes ☐ No
9.1	If no, state the reason	----------
9.2	If no, how many drinks did you miss?	----------

Food Frequency Questionnaire, © JLU Giessen, Institute of International Nutrition
Participant ID.: …….. Date: …… Interviewer:…….. ……

Ulikula nini mwezi jana?

Kinywaji	Drink	Kwa siku	Kwa wiki	Kwa mwezi	Sikunywa	Sijui
Chai (+ maziwa / + sukari)	Tea (+ milk / + sugar)					
Chai (+sukari)	Tea (+ sugar)					
Kahawa (+ maziwa / + sukari)	Coffee (+ milk / + sugar)					
Maziwa	Milk					
Soda	Soda					
Maji	Water					
Juisi	Juice					
Pombe ya kienyeji	Alcoholic drink					
Bia (chupa)	Beer (bottle)					
Konyagi / Gongo	Konyagi / Spirits					
Mvinyo	Wine					

Vyakula vitokanavyo na nyama	Meat and animal products	Kwa siku	Kwa wiki	Kwa mwezi	Sikula	Sijui
Kuku	Chicken					
Ngombe	Beef					
Nguruwe	Pork					
Mbuzi	Mutton					
Bata	Duck					
Ini, moyo, figo	Organ meat					
Dagaa	Sardines					
Samaki mkavu	Dried fish					
Samaki kukaangwa	Fried fish					
Samaki mbichi	Fresh fish					
Mayai	Eggs					
Jibini	Cheese					
Mtindi	Yoghurt					
Vyakula vingine	Other animal products					
Nafaka	**Cereals**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Mahindi-kuchoma	Maize on cob					
Makande	Mix of beans and maize					
Ugali	Stiff porridge					
Uji-mahindi	Porridge from maize					
Uji-mtama	Porridge from millet					
Uji-ulezi	Porridge from sorghum					
Wali	Rice					
Pilau	Pilau					
Chapati	Chapati					
Mkate	Bread					
Mandazi	Donut (Mandazi)					
Vitumbua	Rice cake					

Appendix H: Food frequency questionnaire for pre-diabetic participants

Food Frequency Questionnaire, © JLU Giessen, Institute of International Nutrition
Participant ID.: …….. Date: …….. Interviewer:…… ……

Keki	Cake					
Biskuti	Cookies					
Tambi-makaroni	Spaghetti					
Nyingine (nafaka)	Other cereal					
Vyakula vya mizizi na ndizi	**Roots and tubers**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Viazi vitamu	Potato (sweet)					
Viazi mviringo-mbatata	Potato (irish)					
Chips	Chips/french fries					
Mihogo	Cassava					
Magimbi	Yams					
Cripsi	Crips (fried crackers)					
Ndizi- kupika	Bananas boiled					
Ndizi-kukaanga	Bananas roasted/fried					
Mtori	Bananastew					
Vyakula vingine	Other roots/tubers					
Mboga mboga	**Vegetables**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Bilinganya	Eggplant					
Ngogwe-nyanyacchungu	Tree tomatoes					
Nyanya (kachumbali)	Tomatoes (used in salad)					
Karoti	Carrot					
Maboga	Pumpkin					
Matango	Cucumber					
Karela	Bitter gourd / Karela					
Bamia	Okra					
Chiniz kabichi	Chinese Cabbage					
Kabichi	Cabbage					
Sukuma wiki	Ethiopian kale					
Mchunga	Bitter hare lettuce					
Mchicha	Amaranth leaves					
Kisamvu	Cassava leaves					
Majani ya kunde	Cowpea leaves					
Majani ya maboga	Pumpkin leaves					
Matembele	Other green leafy vegetables					
Mnavu						
Mboga mboga nyingine	Other vegetables					
Mboga jamii ya kunde	**Pulses**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Maharage	Beans					
Dengu	Lentils					
Njegere	Peas					
Njugu mawe	Soybeans					
Choroko	Mung beans					
Nyingine	Other pulses					

Food Frequency Questionnaire, © JLU Giessen, Institute of International Nutrition
Participant ID.: …….. Date: …….. Interviewer:…… ……

Tunda	**Fruits**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Ndizi mbivu	Bananas, ripe					
Maembe	Mangoes					
Machungwa	Oranges					
Tikiti	Melons					
Parachichi	Avocado					
Papai	Papaya					
Nanasi	Pineapple					
Pashen-juice	Passion					
Mbuyu	Baobab					
Zambarau	African Plum					
Nazi	Coconut					
Matunda myingineo	Other fruits					
Mbegu za mafuta	**Nuts and fats/oils**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Margarine (Tan-bond, Blue-band, Sunflower, Flora)	Margarine					
Siagi	Butter					
Kimbo	Kimbo (vegetable fat)					
Lard (mafuta ya wanyama)	Lard (animal fat)					
Tui	Coconut milk					
Siagi ya karanga	Peanut butter					
Korosho	Cashew nuts					
Karanga	Ground nuts					
Mafuta alizeti	Sunflower oil					
Mchanganyiko wa mbegu za mafuta (Korie)	Mixed vegetable oil (Korie)					
Mchikichi	Palm oil					
Viungo- vingine	**Other items**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Jam	Jam					
Asali	Honey					
Sukari ya nyongeza (eg – kwenye juice, kashata,…)	Extra Sugar					
Tomato sauce, chili sauce	Ketchup, chili sauce					
Viungo vya mboga	**Spices**	**Kwa siku**	**Kwa wiki**	**Kwa mwezi**	**Sikula**	**Sijui**
Kitunguu saumu	Garlic					
Nyanya	Tomato					
Tangawizi	Ginger					
Vitunguu maji	Onion					
Pilipili	Chili					
viungo vya pilau	Herbs					
Limao-ndimu	Lemon					
Taja vingine	Something we forgot?					
Tafadhali angalia kama viungo vyote vya chakula vimetaywa hapo juu						

Physical Activity Questionnaire © JLU Giessen, Institute of International Nutrition
Participant ID.: …….. Date: …… Interviewer:…… ……

What activities did you do last week and for how long?

English	Kiswahili	Times per week / mara ngapi kwa wiki	Time used / unatumia Masaa mangapi kila shughuli
General personal activity			
Sleeping (night)	Kulala usiku		
Lying down (nap)	Kulala mchana		
Sitting	Kukaa		
Watching TV	Kuuangalia tv		
Reading	Kusoma		
Computer work	Kazi ya kompyuta		
Time spent supervising children	Kulea watoto		
Time spent on job			
Walking			
Walking to work	Kutembea kawaida kazini		
Walking to market	Kutembea kawaida sokoni		
Walking to friends	Kutembea kwa ndugu		
Walking to church/mosque	Kutembea kawaida kanisa/msikiti		
Walking quickly	Kutembea haraka		
Walking while carrying some load If yes, specify….	Kubeba mzigo Kama ndiyo…		
Riding a bike	Kuendesha baiskeli		
Cooking			
Collecting firewood	Kukata/kutafuta kuni		
Collecting water	Kuchota maji		
Peeling vegetables	Kuchambua mboga		
Kneading dough	Kukanda unga		
Cooking	Kupika		
House work			
Washing clothes	Kufua nguo		
Hanging washing out to dry	Kuanika nguo		
Ironing	Kupiga nguo pasi		
Washing dishes	Kuosha vyombo		
Sewing / knitting	Kushona nguo /kufuma		

Physical Activity Questionnaire © JLU Giessen, Institute of International Nutrition
Participant ID.: …….. Date: …… Interviewer:…… ……

English	**Kiswahili**	**Times per week / mara ngapi kwa wiki**	**Time used / unatumia Masaa mangapi kila shughuli**
House cleaning	Usafi wa nyumba		
Other housework	Kazi nyingine za ndani		
Gardening	Kutunza bustani		
Getting grass for animals	Kukata majani ya kulishia mifugo		
Cleaning staples	Kusafisha zizi		
Milking animals	Kukamua maziwa		
Sports			
Jogging on road or a sports place	Kukimbia (kando kando ya barabara au katika viwanja vya michezo)		
Other sports	Taja michezo mingine		
Any activity we forgot?	Shughuli nyingine		

Drinking instructions – Bitter Gourd Project **1**

The following pictures will help you to follow the instructions on how to prepare and consume the juice. Please remember to always drink it after your main meal.

You will get new water and sachets every week after your appointment at the distribution. Please remember to always bring your bag, calendar and used or remaining sachets to your appointment.

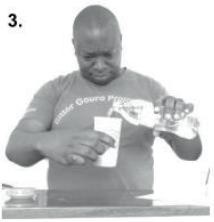
1.

Put the cup on a stable surface and open the sachet.

2.

Pure the powder from the sachet into the cup.

3.



Add 150ml of water to the powder in the cup.

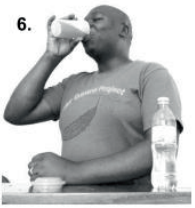
4.

Close the cup properly.

5.

Shake the cup in an upward position until powder is dissolved. If necessary, stir with a spoon.

6.



Drink all of the juice.

7.

After drinking the juice, put a green sticker on the respective date of the calendar. Do only place a sticker if you have drunken the juice.

8.

Rinse the cup thouroughly.

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TANZANIA

National Institute for Medical Research
P.O. Box 9653
Dar es Salaam
Tel: 255 22 2121400/390
Fax: 255 22 2121380/2121360
E-mail: headquarters@nimr.or.tz

Ministry of Health and Social Welfare
P.O. Box 9083
Dar es Salaam
Tel: 255 22 2120262-7
Fax: 255 22 2110986

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12th June, 2013

Dr Mark E Swai
P O Box 345, MOSHI
KILIMANAJRO

CLEARANCE CERTIFICATE FOR CONDUCTING MEDICAL RESEARCH IN TANZANIA

This is to certify that the research entitled: Dietary intervention trial: Single blinded placebo-controlled, randomized study to assess anti-diabetic effect of daily bitter gourd consumption among pre-diabetics at KCRI in Moshi, Tanzania, (Swai M E *et al*), has been granted ethical clearance to be conducted in Tanzania.

The Principal Investigator of the study must ensure that the following conditions are fulfilled:

1. Progress report is submitted to the Ministry of Health and the National Institute for Medical Research, Regional and District Medical Officers after every six months.
2. Permission to publish the results is obtained from National Institute for Medical Research.
3. Copies of final publications are made available to the Ministry of Health & Social Welfare and the National Institute for Medical Research.
4. Any researcher, who contravenes or fails to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine. NIMR Act No. 23 of 1979, PART III Section 10(2).
5. Sites: KCRI, Moshi

Approval is for one year: 12th June 2013 to 11th June, 2014.

Name: Dr Mwelecele N Malecela
Signature
CHAIRPERSON
MEDICAL RESEARCH
COORDINATING COMMITTEE

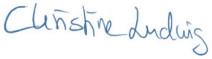
Name: Dr Donan Mmbando
Signature
ACTING CHIEF MEDICAL OFFICER
MINISTRY OF HEALTH, SOCIAL WELFARE

CC: RMO
DMO

Statutory declaration

"I declare: this dissertation submitted is a work of my own, written without any illegitimate help by any third party and only with materials indicated in the dissertation. I have indicated in the text where I have used texts from already published sources, either word for word or in substance, and where I have made statements based on oral information given to me.

At any time during the investigations carried out by me and described in the dissertation, I followed the principles of good scientific practice as defined in the "Statutes of the Justus Liebig University Giessen for the Safeguarding of Good Scientific Practice".



Christine Ludwig
Giessen, January 2016

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VVB LAUFERSWEILER VERLAG

VVB LAUFERSWEILER VERLAG
STAUFENBERGRING 15
D-35396 GIESSEN

Tel: 0641-5599888 Fax: -5599890
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