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Biofortification with zinc in flour for eliminating deficiency

Submission date
28/07/2017

Recruitment status
No longer recruiting

Registration date
02/08/2017

Overall study status
Completed

Last Edited
20/09/2023

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
According to the World Health Organisation, dietary zinc deficiency is a global problem affecting 17% of the world's population, with the greatest burden in developing countries. The most recent national survey in Pakistan indicates that over 40% of women are zinc deficient, compared with less than 15% in Europe and North America. The consequences of zinc deficiency are profound and far reaching, ranging from stunted growth and development in children, increased susceptibility to infections in children and adults, and complications during pregnancy and childbirth. This has a negative economic impact on the family, the community and the region. Various strategies to overcome zinc deficiency have been attempted, but it is difficult to achieve when large populations are concerned. Dietary zinc supplements are expensive and do not always reach the most vulnerable groups who may live in remote or difficult to reach locations due to poor infrastructure or security problems. In contrast, biofortification of staple foods has potential as a sustainable means of increasing population dietary zinc intake. However to date, few studies have been undertaken to evaluate the effectiveness and cultural acceptability of this strategy. One of the key challenges in measuring the effectiveness of such strategies is the lack of a sensitive biomarker of zinc status that is suitable for use in remote settings. A newly developed strain of biofortified wheat has the potential to reach a zinc content that is around 45% higher than the standard varieties. The aim of this study is to examine whether or not consuming the flour made from the high zinc grain has a beneficial impact on the zinc status of zinc-deficient women living in a rural community in North West Pakistan.

Who can participate?
Women aged 16 to 49 living in Peshawar, North West Pakistan

What does the study involve?
Participating families are randomly allocated to consume either the high zinc grain or the standard grain for eight weeks. The families switch over after eight weeks. Blood and hair zinc concentration are measured, along with new indicators of zinc status such as markers of DNA damage and a new portable laser technique for measuring nail zinc concentration. The cultural context, traditions, knowledge and attitudes to biofortification are assessed through focus groups and interviews.

What are the possible benefits and risks of participating?
There are no direct benefits to the participants for taking part in this study. However, it is hoped the information from this study will help to increase understanding of the potential for wheat biofortification to improve zinc status in Pakistan. Specifically this study provides information about the effects of increased zinc intake on nutrition status, growth and health, and on the intestinal bacteria. Risks include temporary bruising at the site of blood sampling. Discomfort may be experienced during tear sample collection. The stimuli used during the dark adaptation test are no brighter than a weak flashlight. They are likely to cause little or no discomfort.

Where is the study run from?
Baghbanan Health Centre (Pakistan)

When is the study starting and how long is it expected to run for?
May 2017 to April 2019

Who is funding the study?
Biotechnology and Biological Sciences Research Council (UK)

Who is the main contact?
Prof. Nicola Lowe

Contact information

Type(s)
Scientific

Contact name
Prof Nicola Lowe

ORCID ID
http://orcid.org/0000-0002-6934-2768

Contact details
Faculty of Health and Wellbeing
230 Darwin Building
University of Central Lancashire
Preston
United Kingdom
PR1 2HE

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
-

Study information

Scientific Title
Examining the effectiveness and acceptability of the use of biofortified crops in alleviating micronutrient deficiencies in Pakistan: a randomised cross over trial

Acronym
BiZiFED

Study objectives
Consumption of flour from biofortified wheat improves zinc status in individuals with marginally deficient dietary zinc intake.

Ethics approval required
Old ethics approval format

Ethics approval(s)
University of Central Lancashire, STEMH Ethics Committee, 11/09/2007, ref: STEMH 697 FR

Study design
Double-blind randomised cross over trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Community

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
ZInc deficiency

Interventions
A double-blind trial will be conducted to examine whether or not consuming the flour made from the high zinc grain has a beneficial impact on the zinc status of zinc deficient women living in a rural community in North West Pakistan.

Randomisation procedure of study area
Stratified cluster sampling with block design. The field study district has 10 hamlets (clusters). Out of these 10 hamlets (clusters), 5 were randomly selected using research Randomiser software. These included:

Cluster 1. Number of Households = 1600 (approx. 500 in each part)
Cluster 2. No. of households = 100
Cluster 3. No. of households = 200
Cluster 4. No. of households = 125
Cluster 5. No. of households = 250

To select an equal number of households from each cluster, each household in each cluster was numbered from 1 to 500, 1 – 100, 1-200, 1-125, 1-250, respectively. The following households were randomly selected from each cluster:

Cluster Randomly Selected Household
1 295, 160, 301, 351, 33, 45, 248, 224, 17, 409
2 19, 67, 46, 58, 45, 66, 83, 42, 34, 57
3 111, 125, 114, 123, 37, 139, 63, 126, 132, 98
4 121, 47, 96, 63, 54, 85, 114, 20, 104, 49
5 247, 180, 248, 182, 14, 167, 166, 36, 201, 157

Selection of each household into the intervention or control arm will be done using a block design.

The high zinc grain will be compared with standard grain, both of which will be provided to 40 families to consume for eight weeks, with group A consuming the high zinc grain and group B consuming the control grain. The families will switch over after eight weeks. To monitor the impact of consuming the flour on zinc status established methods will be used (plasma and hair zinc concentration), and new indicators of zinc status will also be evaluated that have potential for use in population based surveys, including markers of DNA damage and a novel portable laser technique for measuring nail Zn concentration. The success of a biofortification strategy requires that the intervention achieves wide and sustained uptake at production and consumption stages. Therefore, through extensive and established networks with community leaders and farmers, the cultural context, traditions, knowledge and attitudes to biofortification will be assessed in this setting through focus groups and interviews. A key component of this research is training and capacity building. This is a two-way process by which expertise is shared among the project partners, so that young researchers in Pakistan and in the UK are better equipped to take this important research agenda forward into the future, and to build on the collaborative links generated during this project. The findings of this research will be disseminated to researchers and policy makers worldwide.

Intervention Type
Other

Primary outcome measure
Samples are taken for analysis at the end of the equilibration period (week 2), the middle and end of phase 1 (weeks 6 and 10), and the middle and end of crossover phase 2 (weeks 14 and 18):
1. Plasma zinc concentration, measured by inductively coupled plasma mass spectrometry (ICP-MS)
2. DNA fragmentation, measured using the comet assay
3. Hair and nail zinc concentration, measured by laser induced breakdown spectroscopy

Secondary outcome measures

Samples for the following assays are taken for analysis at the end of the equilibration period (week 2), the middle and end of phase 1 (weeks 6 and 10), and the middle and end of crossover phase 2 (weeks 14 and 18):

1. Biochemical markers of nutrient status: haematocrit, haemoglobin, MCV, UIBC, transferrin saturation estimated using clinical haematology methods. Blood samples analysed for micronutrient status including serum transferrin receptor and ferritin (sandwich ELISA), serum Zn and iron (ICPMS), vitamin A (retinol binding protein, commercial kit).

2. Vitamin A status will be assessed by the ability of the eye to adapt in darkness using a portable field dark adaptometer at three time points (during equilibration (weeks 1-2), end of phase 1 (weeks 6-10), and end of phase 2 (weeks 14-18)). Dark adaptometry also called 'night vision test' measures the recovery of visual sensitivity as you go from lit to a dark environment. The process involves briefly exposing the eyes to very bright light and then place a pair of goggles over the eyes for a period of 10 minutes, enabling the eyes to adapt to the dark. Over the following 2 minutes, an LED light in the goggle flashes series of one-second light stimuli into one of the eye, while an infra-red camera records the subject's pupillary response in the other eye.

3. Protein and lipid content of tears will be analysed using proteomics and metabolomics. Tear samples will be collected at three time points (during equilibration (weeks 1-2), end of phase 1 (weeks 6-10), and end of phase 2 (weeks 14-18)) and will be cryopreserved using Schirmer Tear Test (Haag-Streit UK, product number 4701001) strips.

4. Inflammatory markers (α1-acid glycoprotein (AGP) and C- reactive protein (CRP)) will be analysed using commercial kits

5. Anthropometry: Women will be measured at baseline (during week 2) and end point (Week 18). Children in the household will be measured monthly, end of the equilibration period (week 2), the middle and end of phase 1 (weeks 6 and 10), and the middle and end of crossover phase 2 (weeks 14 and 18).

6. Incidence of diarrhoea: Mothers will be asked to keep a continuous record the incidence and duration of diarrhoeal episodes amongst the children of the household throughout the study (weeks 1 to 18)

7. Dietary nutrient intake will be assessed by 24-hour recall and food frequency, interview administered, questionnaire at 3 time points during the study: During the equilibration period (weeks 1-2), at the mid point of phase 1 (week 6) and the mid point of phase 2 (week 10). Data collection will be by interview conducted by the Nutritionist employed on the study.

8. Stool samples will be collected at end of the equilibration period (week 2), the middle and end of phase 1 (weeks 6 and 10), and the middle and end of crossover phase 2 (weeks 14 and 18). These samples will be stored for future microbiome analysis, when further funding is secured.

Overall study start date
01/05/2017

Completion date
30/04/2019

Eligibility

Key inclusion criteria
1. Members of the target community, located on the brick kilns in Peshawar, North West Pakistan
2. Female, aged 16 to 49 years

Participant type(s)
Other

Age group
Adult

Sex
Female

Target number of participants
50 families

Total final enrolment
50

Key exclusion criteria
Pregnant or lactating women

Date of first enrolment
01/09/2017

Date of final enrolment
01/01/2018

Locations

Countries of recruitment
Pakistan

Study participating centre
Baghbanan Health Centre
Pakistan
-

Sponsor information

Organisation
University of Central Lancashire

Sponsor details
Corporation Street
Preston
England
United Kingdom
PR1 2HE

Sponsor type
University/education

Website
www.uclan.ac.uk

ROR
https://ror.org/010jbqd54

Funder(s)

Funder type
Government

Funder Name
Biotechnology and Biological Sciences Research Council

Alternative Name(s)
UKRI - Biotechnology And Biological Sciences Research Council, BBSRC UK, BBSRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The trialists are planning to publish the results of this study in high-impact peer reviewed journals. Papers will be submitted for publication within 1 year of the completion of the overall study, of which this intervention forms a part. The anticipated date for submission of papers is May 2020.

Additional documents (such as study protocol, statistical analysis plan, other) will be available in accordance with the UCLan open access policy which can be found here: http://www.uclan.ac.uk /research/environment/assets/rdm-policy-approved.pdf.

Intention to publish date
01/05/2020

Individual participant data (IPD) sharing plan
The University adheres to an Open Data policy and has an open data repository. Metadata will be collected in the form of “read me” files using basic Dublin Core. Scientific publications will serve to release data into the public domain, and non-confidential data will be available from public data repositories http://uclandata.uclan.ac.uk/. Public release of non-commercially-sensitive material will be concurrent with publication, or prior to this when publication is not compromised, with the agreement of all partners. Data release will be under a “cc-By” licence. The data that will be made available will be anonymised in accordance with the participant consent form. The types of data that will be made available include:
1. Biochemical data. This project will generate a low volume of personal data from the analysis of blood, hair, tear and nail samples. Final datasets will be made available in the form of Excel spreadsheets.
2. Physiological data: Anthropometry, dark adaptation, diarrhoeal incidence. Final datasets will be made available in the form of Excel spreadsheets.
3. Dietary data: Nutrient intakes and dietary diversity data. Final datasets will be made available in the form of Excel spreadsheets.
4. Questionnaire data. Anonymised data will be made available, summarised in the form of Excel spreadsheets.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	17/04/2018		Yes	No
Results article	results	17/09/2020	05/11/2020	Yes	No
Results article	results	01/10/2020	10/11/2020	Yes	No
Results article		17/01/2017	20/09/2023	Yes	No
Results article		06/11/2020	20/09/2023	Yes	No
Results article		18/01/2022	20/09/2023	Yes	No