The Impact of Zinc Levels on Taste Change and Hair Loss Following Bariatric Surgery and Reporting of Dietary Compliance to Weight Loss Interventions

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In the name of Allah, The Most Gracious and The Most Merciful

Declaration

I declare that the work included in this thesis is entirely mine and has not been previously submitted for any other degree. At the Division of Medical Sciences & Graduate Entry Medicine at the School of Medicine, University of Nottingham, Royal Derby Hospital. Professor Iskandar Idris and Dr Philip Atherton are supervising this effort.

Boshra Mozaffar

Covid-19 Statement

On March 2020, I was ready to submit my protocol to get ethical approval and begin my clinical work in the UK as a part of my PhD thesis, when news of an epidemic of a novel coronavirus (COVID-19) outbreak was reported. The widespread shutdown of universities rendered it impossible for students to begin clinical work at the University during the (COVID-19) epidemic. During the lockdown time I performed a systematic review and meta-analysis to explore the effectiveness of zinc supplementation in taste change improvement. With support and approval from my supervisor, we managed to obtain ethical approval for my project to commence in one of my own country's hospitals (King Abdullah Medical City). I began collecting data in February 2021. Unfortunately, the process of data collection was repeatedly delayed owing to a rise in cases of COVID-19 in the hospital, which negatively impacted the number of bariatric procedures performed, rendering it impossible to acquire baseline data. My data collection was negatively influenced by the lack of time to finish this portion of the study and the psychological impact of COVID-19. Yet, through self-motivation and perseverance, I worked tirelessly to overcome these obstacles.

Acknowledgements

This work is devoted to Allah, the Most Merciful and Forgiving who made it possible for me to accomplish my journey and achieve my objectives. I am grateful to everyone who has assisted me in pursuing my ambition of achieving my dream of becoming a PhD. This endeavour would not have been possible without the support of my family who gave me life, strength, determination, and hope. Words cannot express the gratitude I have for my mother Fawziah and father Mohammed who have supported me throughout this process and sustained me in moments of weakness and strength. I am also extremely grateful to my sisters, my brothers, and my niece. Special thanks to my sister Ebtisam for her help and support. This work is dedicated to my children Jawad, Sanad, and Rand who have made me stronger, better, and more joyful than I ever dreamed possible; I love you to the moon and back.

Special thanks to my supervisor, Professor Iskandar Idris for his time, effort, and knowledge in assisting with the preparation of this dissertation. Additionally, I wish to express my heartfelt gratitude to all my research department colleagues, the PGR coordinators, and all of the PGR students who have unfailingly assisted me throughout this study. Finally, I would like to acknowledge my sponsor, Jazan University, and the Royal Embassy of Saudi Arabia Cultural Bureau, who supported me and provided me with the opportunity to complete my PhD studies.

Abstract

Currently, there is significant interest in the effective treatment of obesity, particularly the implementation of a very low-calorie diet (VLCD) and the use of bariatric surgery (BS) which is a well-established long-term treatment. However, much of the contemporary research has noted that patients who have undergone bariatric surgery have reported unexplained side effects, such as a change in their sense of taste which may impact dietary compliance post-surgery. Additionally, there is limited research concerning long-term compliance with a very low-calorie diet which is a crucial aspect of pre-and post-bariatric surgery eating requirement. This thesis is divided into two sections: the first section investigates the links between taste change and zinc following BS, and the second section examines patients' compliance with a VLCD. The over-arching theme of the thesis focuses on the speculative association of taste and hair loss following bariatric surgery with decreased circulating zinc levels, which might affect compliance to post-surgery eating requirements and the reporting of compliance to significant calorie restriction. In the initial part of the first section, a systematic review was conducted to collect evidence regarding the role of zinc in the development of taste disorders among patients who had undergone bariatric surgery and those who had not. This study used PRISMA guidelines to conduct systematic reviews of several electronic bibliographical databases, including EMBASE, PubMed, AMED, and MEDLINE, for studies concerning the effects of BS on taste, the effects of BS on zinc levels, and the effect of zinc replacement on taste. The results from this systematic review demonstrated that, according to the findings of qualitative research (conducted via questionnaires), taste change was observed in the majority of patients within a year following bariatric surgery. However, experimental investigations did not yield statistically significant evidence of taste alteration. A total of twelve investigations were conducted to examine the occurrence of zinc deficiency following bariatric surgery (BS),

which revealed a notable reduction in zinc levels that persisted for six months post-surgery. The administration of zinc sulphate was found to be efficacious in enhancing taste perception in patients, apart from those with a cancer diagnosis who did not exhibit any improvement in taste following the dispensation of zinc supplements.

Given that zinc deficiency and taste disorders occur in repeated cases at approximately the same time, this study hypothesises the existence of a potential relationship between these two factors. Therefore, the subsequent section of this work examines the connection between zinc and taste change following sleeve gastrectomy (SG) and gastric bypass (GB) via a single-centre, prospective cohort study conducted at King Abdullah Medical City (KAMC) in Saudi Arabia (Makkah). Forty-three patients were selected, consisting of eighteen gastric bypass patients and twenty-five patients who had undergone sleeve gastrectomy (SG). The duration of the follow-up period spanned a length of six months. The assessment of taste alteration was conducted via the utilisation of a validated questionnaire and implementation of the taste strips technique. Additionally, the study involved the measurement of serum zinc levels and salivary flow rate for all of the participants.

Following the administration of the questionnaire, the results of this study demonstrate that patients who had undergone gastric bypass (GB) surgery exhibited a higher prevalence of hypogeusia (at the three-month mark) when compared with those who underwent sleeve gastrectomy (SG), with percentages of 72.0% and 36.0% respectively ($p=0.03$). However, no significant difference in hypogeusia prevalence was discovered between the two groups at the six-month mark, with percentages of 56.0% for GB and 45.0% for SG patients ($p=0.74$). However, when taste strips were utilised, there was no notable disparity in the occurrence of hypogeusia between patients with GB and SG at the three-month point (44.4% versus 36.0%,

p=0.75). Nevertheless, at six months, a higher proportion of patients with GB reported experiencing hypogeusia compared to SG patients (44.0% vs. 11.0%, p=0.052). The study observed a significant decrease in zinc levels among GB patients, from the initial measurement of 85.6±16.9µgm /dl to the six-month measurement of 67.5±9.2µgm/dl. Conversely, SG patients reported an increase in zinc levels from the baseline measurement of 76.9±11.4 to the six-month measurement of 84.9±21.7µgm/dl. A decrease in the salivary flow rate was noted in 66.0% and 72.0% of individuals with GB and SG, respectively, after 3 months, and in 47.0% and 70.0%, respectively, after 6 months.

Hair loss was noted as an additional side-effect following BS; however, the underlying causes and factors of this condition remain unidentified. Therefore, a subsequent section investigates the potential association between hair loss and decreased circulating zinc levels following BS and the differences between SG and GB patients. The findings of the study revealed that the prevalence of hair loss among patients who underwent GB was double that of SG. Specifically, at three months post-surgery, the percentage of hair loss was 66.6% in the GB group and 32% in the SG group, indicating a significant difference between the two groups (P = 0.025). Furthermore, at six months post-surgery, the percentage of hair loss increased to 75% among GB patients, while it decreased to 20% among SG patients. The findings also indicated a statistically significant difference between the groups, with a p-value of 0.001. This research established that individuals who had undergone bariatric surgery and experienced subsequent hair loss displayed reduced zinc levels compared to the established reference value and that, in this patient population, females were more susceptible to hair loss than males.

These findings suggest that hair loss is a frequently observed adverse outcome that can occur following both types of surgeries; however, it has been shown that GB patients are inclined to

experience a higher degree of hair loss, which has been linked to lower levels of zinc in their blood.

In the final part of this section, a study assessed the effective zinc doses for taste disorder treatment to inform future clinical guidelines and studies regarding the use of zinc as a remedy for taste disorders following BS. A systematic review and meta-analysis were conducted regarding the effectiveness of zinc supplementation in taste disorder treatment following the guidelines outlined in the PRISMA Statement. A comprehensive search of four electronic bibliographic databases (Ovid MEDLINE, Ovid Embase, Ovid AMAD, and PubMed) was conducted. This review has been duly recorded with PROSPERO and assigned the unique identification number CRD42021228461. The results demonstrate that zinc supplementation, when administered at high dosages ranging from 68 to 86.7 mg/d for a duration of up to six months, is an efficacious intervention for taste abnormalities in individuals with zinc deficiency, idiopathic taste disorders, and those with taste disorders resulting from chronic renal failure.

The second section of this thesis concerns a clinical study involving thirty-five, healthy, middle-aged male volunteers and is designed to investigate and document the consumption of an extra calorie allowance derived from conventional foods or only from vegetables and nuts (up to 200kcal/day). Additionally, this study employed two distinct evaluation methodologies to analyse the macronutrient composition of these dietary additions to evaluate VLCD compliance for up to six weeks. The results revealed that patients following a very low-calorie diet (VLCD) who are provided with an additional food allowance from traditional sources or have their food intake confined to vegetables and nuts, frequently consume more calories than

the prescribed daily limit. How compliance is reported exhibits substantial variation depending on the method of monitoring employed.

The data presented in the conclusion of this thesis suggest that: firstly, decreased circulating zinc level following bariatric surgery is directly correlated to taste change, low salivary flow and hair loss, and that high doses of zinc supplementation are an effective remedy for taste change; and, secondly, patients fail to strictly adhere to VLCD. Additionally, the data presented by this thesis suggests that future research concerning the effectiveness of zinc supplementation in taste disorder treatment (following bariatric surgery), and additional studies concerning long-term compliance with a very low-calorie diet, are required.

List of Publication

Published peer-reviewed scientific papers:

Mozaffar, B., Ardavani, A., Muzafar, H., & Idris, I. (2023). The Effectiveness of Zinc Supplementation in Taste Disorder Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Nutrition and Metabolism,* 2023.

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Ardavani A, Aziz H, Phillips BE, Doleman B, Ramzan I, **Mozaffar B**, Atherton PJ, Idris I. Indicators of response to exercise training: a systematic review and meta-analysis. *BMJ Open*. 2021.

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Prizes

I was awarded the first-place prize for a poster titled “Zinc as a contributor of taste change associated with bariatric surgery” in the BOMSS 2023 conference held at Hilton Birmingham Metropole on 5th -7th June 2023.

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List of Abbreviations

AGB	Adjustable gastric banding
BMI	Body Mass Index
BOMSS	British obesity and metabolic surgery society
BS	Bariatric Surgery
BPD	Biliopancreatic diversion
COVID-19	Corona Virus Disease of 2019
DS	Duodenal switch
EWL%	Excessive weight loss percentage
EBMI%	percentage of excess BMI loss
EI	Energy intake
FFQ	Food-frequency Questionnaires
TBs	Taste buds
TRCs	Taste receptor cells
TWL%	percent of total weight loss
GB	Gastric bypass
GLP-1	Glucagon-Like Peptide-1
GERD	Gastroesophageal reflux disease
GJ	Gastro-jejunal
GPCR	G protein-coupled receptors
IFSO	International Federation for The Surgery of Obesity and Metabolic Disorders
KAMC	King Abdulla Medical City

KSA	Kingdom of Saudi Arabia
LCD	Low calorie diet.
MDTs	Multidisciplinary teams
MGB	Mini-Gastric bypass
MSG	Monosodium glutamate
PYY	Peptide tyrosine tyrosine
RCT	Randomized controlled trails
RDA	Recommended dietary allowance
RYGB	Roux-en-Y gastric bypass
NHS	National Health Service
NICE	National institute for health and care excellence
SF	Salivary flow
SG	Sleeve gastrectomy
VAS	Visual Analogue Scales
VLCD	Very Low-Calorie Diets
UK	United Kingdom
WHO	World Health Organization
WR	Weight regains
24HR	Food Record and 24-hour dietary recall

Chapter 1: Introduction

1. Introduction

1.1. Obesity

Obesity has developed into a major, ongoing health concern and is the most rapidly growing disease around the globe. The World Health Organisation (WHO) defines obesity (or being overweight) as an accumulation of adipose tissue (or body fat) in the human body which impacts people's health and quality of life [1]. It can cause numerous life-threatening health conditions including chronic diseases (such as hypertension, diabetes, and heart disease), some forms of cancer (such as breast and bowel cancer), strokes, asthma, gallstones, sleep apnoea, kidney disease, liver disease and metabolic syndrome [2]. Additionally, it can induce other health problems including breathlessness, increased perspiration, snoring, back pain, and difficulty engaging in physical activity [3, 4]. Obesity can also cause psychological impacts such as depression, reduced levels of confidence and feelings of isolation [5].

Nevertheless, it is important to note that not all types of obesity provide the same level of risk [6]. Certain individuals, while having higher levels of body fat, are less susceptible to certain chronic consequences associated with obesity. Evidence indicates that the specific placement of fat in the body and the overall condition of fat significantly impact the likelihood of developing diseases [7]. For instance, having more visceral fat compared to subcutaneous fat is linked to increased metabolic risk [8, 9]. Therefore, comprehending the factors that influence the deposition of fat tissue can offer valuable knowledge on the harmful effects of obesity and can help identify potential strategies for innovative treatments to address the widespread issue of obesity. Interestingly, in a study investigating the effect of bariatric surgery on body composition and fat distribution, it was observed that the proportion of visceral to subcutaneous abdominal fat remains rather stable 6 months after bariatric surgeries, regardless of gender,

kind of treatment, or the occurrence of metabolic problems. An improvement in metabolic parameters however is linked to a decrease in the ratio of visceral fat to abdominal fat [10].

According to WHO, there is a significant global prevalence of obesity, with around 650 million people, 340 million teens, and 39 million children falling into this category. Furthermore, it is projected that these figures will continue to climb in the future. Additionally, WHO has indicated that a projected 167 million individuals, including both adults and children, are expected to encounter declining health conditions by the year 2025 due to the presence of excess weight or obesity [1].

The Active Lives Adult Survey (2022), which contains the most up-to-date obesity statistics in England, identified over one year (November 2020 to November 2021), that 25.3% of UK adults (18 and over) were living with obesity [11]. According to the Kingdom of Saudi Arabia (KSA) World Health Survey, 20.2% of the adult population is living with obesity and 38.2% are living with being overweight. Additionally, the statistics revealed that there are more women in Saudi Arabia than men living with obesity; 21.4 % of women are living with obesity and 32.7% are overweight, while 19.2% of men are living with obesity and 42.7% are overweight [12].

Customarily, obesity occurs via the ingestion of more calories (particularly those found in high-fat and high-sugar food which causes the body to store excess energy as fat) than are burnt off via exercise. Other causes of obesity among adults include a poor diet, lack of physical activity, genetics, and medical reasons [13]. The measurement of obesity can be conducted using the Body Mass Index (BMI) standards, which have defined five distinct categories for body weight: healthy body weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), obesity class I

(30-34.9 kg/m^2), obesity class II (35-39.9 kg/m^2), and obesity class III (40 kg/m^2). When undertaking a comparative analysis of various ethnic groups, it is important to acknowledge that the Body Mass Index (BMI) may not accurately reflect the true representation, particularly in populations characterised by significant diversity [14].

Treatments for people living with obesity and overweight include the promotion of healthy eating practices, regular exercise, weight management programs, weight-loss medications, and weight-loss devices. Weight management programs may encourage weight loss or prevent weight gain, however, some people with obesity are unable to maintain their weight loss or reduce their weight enough to enhance their health. In these circumstances, a physician may consider alternative therapies such as weight-loss drugs, weight-loss devices, or bariatric surgery [15]. A recent area of interest concerns placing the patient on a very low-calorie diet (VLCD) which incorporates nutritionally complete meal replacement products [16].

1.2 Very Low-Calorie Diets (VLCD)

Since their inception, the definition of calorific restriction attached to Very Low-Calorie Diets (VLCDs) and Low-Calorie Diets (LCDs) has been amended. VLCDs were first introduced in a 1929 study which introduced a dietary regimen consisting of food elements totalling approximately 400 kcal which aimed to accelerate weight reduction. By VLCD, instead of implementing a dietary restriction of 14 to 15 kcal/kg for those with obesity (leading to weight reductions of 2.5 to 3.5 kg per month), the researchers opted for a more accelerated approach by cutting the energy intake to 6 to 8 kcal/kg [17]. Currently, the definition of VLCD is classified as total diet replacements that provide less than 800 kilocalories per day, but more than 400 to 450 kilocalories per day accompanied with a modified distribution of macronutrients and a set composition of micronutrients [18, 19]. VLCDs are often prescribed for patients with a BMI above 30 kg/m^2 who have been unsuccessful in losing weight with

LCD [20]. LCDs are defined as dietary regimens that typically provide a daily caloric intake that ranges from 800 to 1200 kcal [21]. A complete nutritional profile of vitamins and minerals, combined with a balanced macronutrient profile, has been associated with significant health benefits [22, 23]. According to NICE recommendations from 2014 [24], the dietary guidelines in the United States suggest that VLCDs should only be used for weight loss in individuals living with obesity under specific conditions. These conditions include being supervised by experienced professionals in a medical care facility, where the individual can receive medical monitoring and intensive lifestyle intervention [25]. VLCDs are not advised for the general population owing to insufficient evidence. Due to the significant dangers of malnutrition associated with an improperly formulated or unsupervised VLCD, those undertaking such diets must be regularly monitored by a medical professional to avert any consequences [26].

Several studies [27] have established that the maximum rate of weight reduction in VLCDs and LCDs is approximately 2.5kg per week (within the initial four to six weeks of the intervention). However, in longer-term intervention trials, the use of VLCDs was examined for a duration of up to six months and demonstrated that, after the initial six-week period, the rate of weight loss decreased to roughly 0.8 kg per week and remained consistent thereafter [27]. A systematic review of a VLCD intervention period of five days to six months revealed that weight loss varied between 4.1 and 24kg (an average loss of 13.2 kg). Nevertheless, the post-intervention evaluation period, ranging from eight days to five years, revealed that weight regain following the termination of VLCDs varied from 2 to 14 kg [28]. The VLCD which has a daily caloric intake of 450–800 kcal, was connected with preoperative weight loss of 10% and BMI reduction of 9% [29]. Another study compares the effects of weight reduction between a balanced hypocaloric diet and a VLCD after two months of therapy and evaluates the long-term weight maintenance and safety over a period of 26 months with and without VLCD support in individuals living with obesity, found that in the first two-month timeframe,

the average reduction in body weight for the VLCD group was 18.9 ± 7.1 kg, while the diet treatment group saw a weight loss of 7.2 ± 4.8 kg. The relative fat loss, as measured by bioimpedance, was found to be 68% and 76% for the VLCD and diet treated groups, respectively. The average weight reduction that was sustained after 28 months of therapy was 10.9±10.2 kg among the 52% of individuals who successfully finished the regimen [30]. When individuals consistently follow a weight reduction plan over a longer period of time, significant initial weight loss can lead to successful long-term weight maintenance in motivated individuals [31].

1.3 Bariatric surgery

1.3.1 The Prevalence of Bariatric Surgery and its Health Benefits

Bariatric surgery (BS) has emerged as the most economically efficient intervention for addressing obesity. Based on the global registry report of bariatric surgery conducted by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO), it has been observed that a total of 72,645 Roux-en-Y gastric bypass (RYGB) surgeries (38.2%), 87,467 sleeve gastrectomy (SG) operations (46.0%), 14,516 one-anastomosis gastric bypass procedures (7.6%), and 9,534 Adjustable gastric banding (AGB) operations (5.0%) have been performed worldwide since 2014 [32].

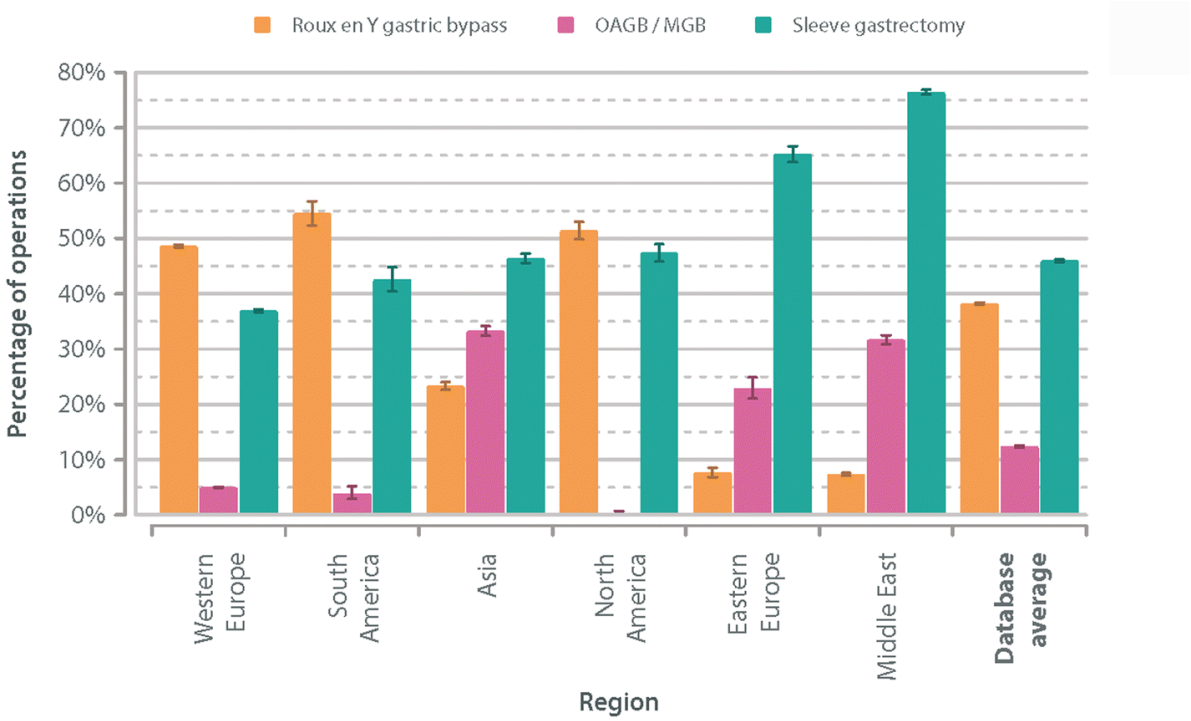


Figure 1.1 Types of operation - data by region for 2014-2018 [32].

Following BS, there is a noticeable improvement in the treatment of diabetes, hypertension, sleep apnoea, arthritis, and metabolic syndrome [33, 34]. When compared with diet and medicine, this surgical obesity treatment has proven to be more successful in achieving sustained weight loss in individuals living with severe obesity [35].

Different definitions have been employed in the bariatric literature to document weight reduction and provide criteria for weight loss and weight regain [36, 37]. The percent excess weight loss (%EWL) is determined by calculating the amount of weight loss that exceeds the ideal body weight [38]. Bariatric associations have suggested utilising a BMI of 25 kg/m^2 as a standard for determining weight reduction. Thus, starting from 2005, %EWL and percentage of excess BMI loss (%EBMI) have been equivalent in measuring the amount of excess BMI decrease [39, 40]. Based on this, an effective result of bariatric surgery is therefore defined as a reduction of 50-70% of the excess weight or a decrease of 20-30% from the patient's baseline

weight, resulting in a BMI below 35 kg/m^2 [41, 42]. In another research authors defined EWL as reaching to less than or equal to BMI 18.5kg/m^2 at any time until 24 months after surgery [43]. Previous publications assert that percent of total weight loss (%TWL) is potentially the most precise indicator for evaluating weight reduction among individuals who have had BS [44]. In a study aimed to examine the reliability of two clinically prevalent indications, %TWL and %EWL, by comparing their performances in predicting metabolic syndrome remission one year following bariatric surgery, authors found that good responders to bariatric surgery should be defined as those exhibiting %TWL ≥ 25% [45]. For multiple reasons; a study found that %EWL were unsuitable for comparing non-randomized groups or various patients [46]. In addition, Using TWL may provide a more precise result without requiring the specification of ideal body weight. Moreover, %TWL is little affected by the starting BMI, which might operate as a confounding variable[45].

In spite of the fact that several studies have demonstrated the capability and efficacy of bariatric surgery in decreasing excess weight in the short term, investigations conducted over an intermediate and longer period of time have indicated that weight recovery is an indicator of failure of the surgery [47, 48]. There is currently no unanimous agreement on which measure should be employed to determine a satisfactory or unsatisfactory response to bariatric surgery in terms of weight regain. Several criteria for weight return in the literature have been offered [49]. These include a rise in BMI to 35 kg/m^2 or higher after previously having a BMI of 35 kg/m^{2}or below, regaining more than 25% of excess weight loss (EWL) from the lowest point [50], having EWL less than 50% after previously achieving at least 50% EWL and sustaining more than 20% TWL [51].

BS has been linked to a considerable decrease in overall mortality [52]. Due to the existence of several co-morbidities that heighten the potential risk, it is strongly suggested that obese patients receive a preoperative examination before undergoing any type of surgery [53]. The

Saudi clinical practice guidelines, similar to the American Society for Metabolic and Bariatric Surgery [54], and NICE guidelines that apply in the UK, recommends that patients are required to meet following criteria for eligibility to be considered for BS: a BMI of 40 kg/m^2 or higher or between 35 kg/m^2 and 40 kg/m^2 with other obesity related co-morbidities such as type 2 diabetes, hypertension obstructive sleep apnoea and that all non-surgical options must have been exhausted, despite which, individual has not achieved or sustained a clinically desirable outcome [24].

1.3.2 Varieties of Bariatric Surgery

Bariatric surgery can assist weight loss via two methods: restriction (which reduces the amount of food that the stomach can hold and restricts the number of calories consumed) or malabsorption (which reduces the number of calories and nutrients a body can absorb via bypassing or shortening, a section of the small intestine). When undergoing bariatric surgery, a patient may receive one of the following: gastric sleeve, gastric bypass, duodenal switch**,** gastric balloon or gastric band [55]**.** Globally, the most common bariatric procedures are a sleeve gastrectomy and a gastric bypass [56].

1.3.2.1 Sleeve gastrectomy (SG)

Sleeve gastrectomy (SG) is a single-stage therapy for obesity, routinely performed to decrease calorie intake and bypass intestinal absorption processes. An SG involves the removal of a major piece of the stomach, resulting in reduced stomach capacity. This procedure contains inherent risks including blood clots, vitamin or iron deficiency, skin separation, leakage, stomach or intestinal perforation, internal bleeding, profuse bleeding of the surgical wound, hernias, and gallstones [57, 58].

1.3.2.2 Gastric bypass (GB)

A gastric bypass (GB), also known as a Roux-en-Y gastric bypass (RYGB), can be offered to patients with morbid obesity who are aiming to reduce their unhealthy body weight by 65 to 90 per cent. It is considered to be a suitable procedure for patients diagnosed with Type 2 diabetes who require a long-term solution [59] because it is arguably more effective than SG in the treatment of this condition. Additionally, GB is an effective treatment for acid reflux, heartburn, and gastroesophageal reflux disease (GERD) [60]. A gastric bypass divides the stomach into two distinct pouches, following which the small intestine is altered to link to both the small top pouch and the larger, bottom, remnant pouch. There are many gastric bypass surgeries and all of them are malabsorptive (although some are also restrictive). The most common variety of gastric bypass is the RYGB, and the least common is a Biliopancreatic Diversion Gastric Bypass although recently, the Mini Gastric Bypass (MGB) has risen in prominence. Regardless of which technique is adopted, they all bypass the small intestine, and some of them reduce the size of the stomach.

Any GB results in a considerable decrease in the functional volume of the stomach, as well as altering the physiological and physical responses to meals [61, 62]. This technique is recommended for the treatment of comorbid conditions including Type 2 diabetes, hypertension, sleep apnoea, and morbid obesity (defined as a BMI over 40) [63].

Similar to other surgical procedures, gastric bypass surgery (GB) carries certain risks. These risks include the possibility of device breakage, the occurrence of dumping syndrome, an increased likelihood of developing gallstones after experiencing rapid or significant weight loss, the potential for hernias, internal bleeding or excessive bleeding at the surgical site, leakage, stomach or intestinal perforations, bowel obstruction, protein or calorie malnutrition,

pulmonary and/or cardiac complications, skin separation, injury to the spleen or other organs, stomach or intestinal ulceration, stricture formation, and deficiencies in vitamins or iron [64].

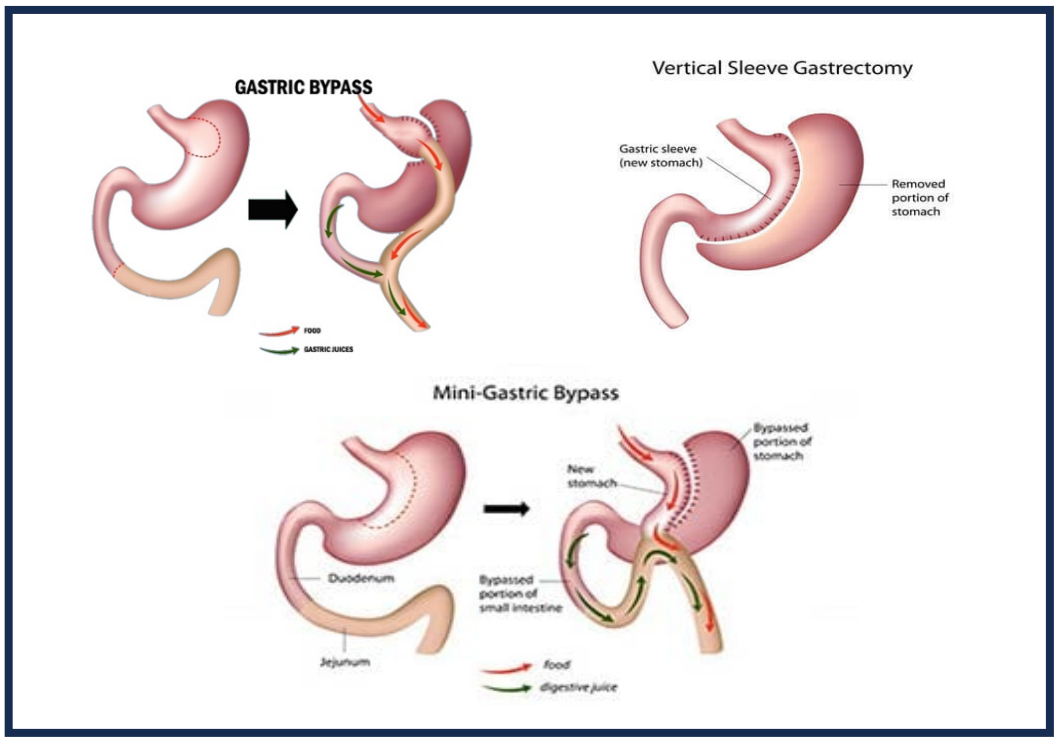


Figure 1.2 The differences between sleeve gastrectomy, gastric bypass, and mini-gastric bypass. Modified from https://www.bariatric-surgery-source [65].

1.3.3 Micronutrient Deficiency Before Bariatric Surgery

Prior to BS, patients living with obesity frequently present with a nutritional deficiency due to a poor-quality diet that contains excessive calories and an imbalanced nutritional composition [1, 66]. One study involving female patients undergoing BS revealed that despite consuming a high-caloric diet (2800 kcal/day), 66% of the participants were affected by at least one micronutrient deficiency. This was the case even though all of the participants had elevated levels of overall caloric intake [67]. Additionally, before prior to BS, 20% presented with low iron levels and 21.5% were anaemic [68].

1.3.4 Micronutrient Deficiency Following Bariatric Surgery

During the first six months following BS, rapid weight loss is very prevalent and increases the likelihood of micronutrient deficiency [69]. Many factors can cause the development of nutritional deficits following BS including non-compliance with dietary supplements (not remembering to take the prescribed supplements and difficulty in swallowing the medication) [70]; irregularity of long-term follow-up after BS [71]; food intolerance; inferior eating habits; vomiting; and changes in taste and eating patterns. Additionally, patients may experience a deficiency of water-soluble vitamins following the loss of gastrointestinal segments that are responsible for the absorption of nutrients [72].

British Obesity and Metabolic Surgery Society (BOMSS) Guidelines recommend taking a comprehensive multivitamin and mineral supplement (including iron, selenium, zinc, and copper) after all forms of bariatric surgery to prevent micronutrient deficiencies. Following gastric banding surgery, the BOMSS advises an iron intake of 45–60 mg per day via multivitamins and mineral supplements. In addition to the multivitamin and mineral supplements, patients undergoing SG or GB treatments require an extra iron intake of up to 200 mg ferrous sulphate, 210 mg ferrous fumarate, or 300 mg ferrous gluconate per day [73]. The minimum daily iron requirement for menstruating women is 100 mg (two ferrous sulphate or ferrous fumarate supplements). The BOMSS suggests that multivitamins and mineral supplements contain the appropriate amounts of zinc and copper. A ratio of between 8 and 15 milligrams of zinc per two milligrams of copper should be maintained if more zinc is necessary. Patients undergoing GB, Biliopancreatic diversion (BPD) or dialysis sequestration require extra zinc and copper supplements (2 mg copper and 15 mg zinc per day) [73].

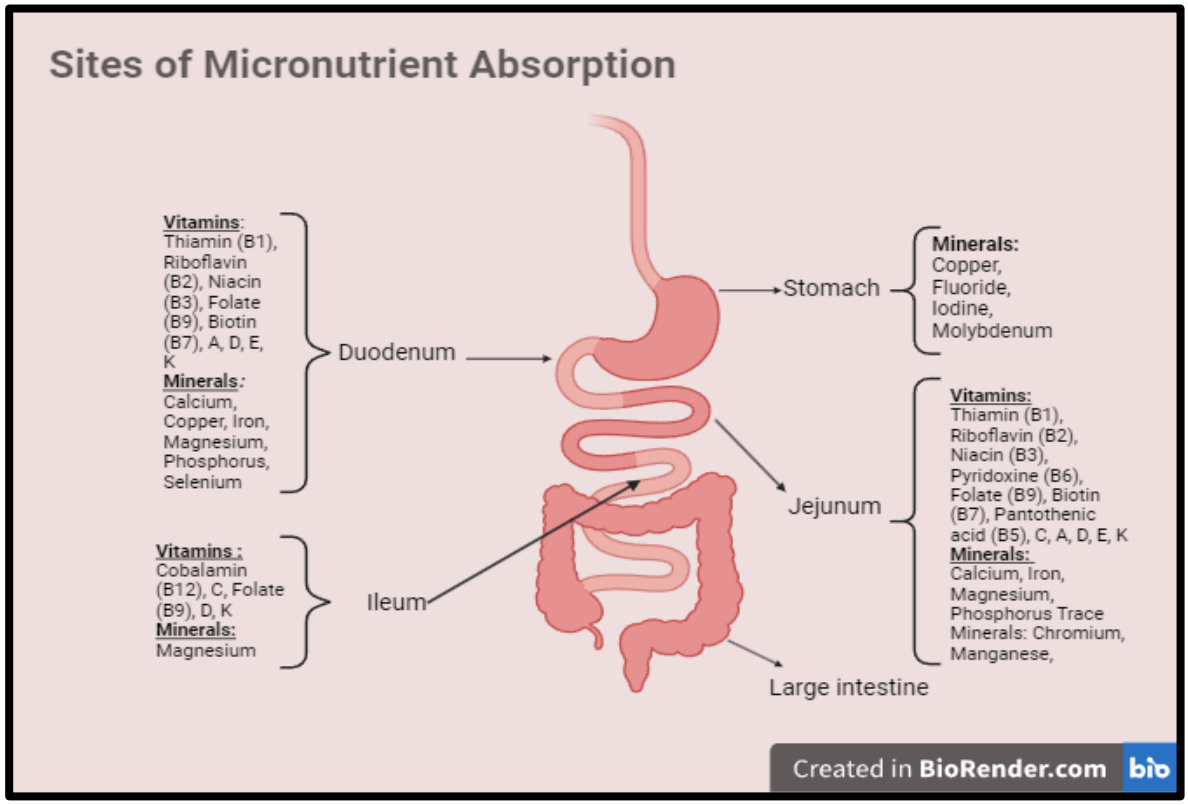


Figure 1.3 Sites of Absorption of Vitamins, Minerals and Nutrients.

Created with BioRender.com - modified from https://epomedicine.com/medical-students/site-absorption-vitamins-minerals-nutrients/) [74].

Following BS, patients may experience zinc malabsorption [75] leading to zinc deficiency [76]. Zinc deficiency is characterised by an inadequate amount of zinc to fulfil the body's requirements, or by a blood zinc level that falls below the normal range [77]. Zinc deficiency in humans can be brought on by a decrease in food intake, insufficient absorption, increased loss, or increased utilisation of metabolic processes inside the body [78]. The most prevalent cause is a decrease in the amount of food consumed [79]. Zinc deficit is uncommon following RYGB surgery. It is recommended to consider zinc deficiency in patients who present with skin lesions, hair loss, dysgeusia, hypogonadism, or unexplained iron deficiency anaemia [80].

The recommended dietary allowance (RDA) for zinc differs according to different organisations, The Institute of Medicine recommends 8 mg/d for females receiving a mixed diet and 11 mg/d for males; the European Food Safety Agency recommends 7.5-12.7 mg/d for females and 9.4-16.3 mg/d for males, with the amount depending on the phytate in the diet. The recommended daily intake of WHO is 3.0-9.8 mg/d for females and 4.2-14.0 mg/d for males, with a bioavailability of 50% and 15% accordingly [77]. Zinc may be quantified in many biological samples such as whole blood, plasma, serum, urine, or hair, preferably using atomic absorption spectroscopy [81]. Plasma zinc measurement is the most often used test to confirm clinical zinc deficiency and evaluate the adequacy of zinc intake [82]. However, previous studies found that plasma zinc levels alone are not conclusive for determining zinc deficiency or body status and recommended plasma zinc levels should be accompanied by zinc concentration measurements in nucleated tissues such liver, muscle, or bone as zinc-dependent enzymes may not consistently indicate the level of zinc in the body [83, 84]. In addition, over the course of 24 hours, the levels of zinc in the blood of individuals who consume meals orally might fluctuate by as much as 20%, primarily as a result of food consumption. It is essential to analyse the data while considering the variations in serum albumin levels and the magnitude of the inflammatory response [78]. The typical range of zinc content in blood or plasma for persons in a state of well-being is 80 to 120 mcg/dL (12 to 18 mcmol/L) [79]. Zinc readings below 70 mcg/dL in women and 74 mcg/dL in males suggest insufficient zinc levels [85]. Zinc is generally regarded as being very non-toxic, especially when used orally. Nevertheless, the occurrence of clear and evident signs of poisoning, such as nausea, vomiting, epigastric discomfort, lethargy, and weariness, will only happen when zinc intake reaches exceptionally high levels. [86]. Among the most abundant dietary sources of zinc are seafood, poultry, and fish [87]. Oysters have the highest concentration of zinc per serving compared to any other meal [88]. Zinc is also present in eggs and dairy products [87]. Zinc may be found in beans,

nuts, and whole grains; however, due to the presence of phytates, the amount of zinc that can be absorbed from these foods is lower than the amount that can be absorbed from animal foods. Phytates, which are the form of phosphorus that is retained in plants, bind themselves to certain minerals in the gut, such as zinc, and generate a solid complex that hinders the absorption of zinc. Red meat and poultry are important source of zinc. This diet is highly consumed in UK and Saudi Arabia [79, 84, 85, 89].

1.3.5 Taste Change Following Bariatric Surgery

1.3.5.1 Physiological and hedonic domains of Gustation (Taste)

In today's world, the consumption of food no longer just serves as the means to preserve function and maintain physiological integrity; rather, it now also serves the purpose of satisfying hedonic wants [90]. Hedonic food intake, also known as the ingestion of food for the purpose of achieving pleasure and palatability [91], is the consequence of a complex interaction between sensory perceptions, with taste being an essential component of this interaction [92] and plays an important role in dietary compliance to induce weight loss. Taste, commonly referred to as gustatory perception or gustation, is one of the five recognised senses [93]. The gustatory system is a complex network that include dopaminergic pathways to initiate reactions, detect taste stimuli, and engage cognitive processes for stimulus recognition. [94]. It consists of taste receptor cells (TRCs) located on the taste buds (TBs) and distributed among thousands of different papillae on the human tongue [95]. Taste buds have an average lifespan of approximately ten days [96]. Taste receptors are found in several areas of the mouth, including the epiglottis and the top surface of the tongue. Taste sensation occurs when substances in the oral cavity interact with taste receptor cells (TRCs) [97]. Taste may be categorised into five groups based on behaviour: bitter, salty, sweet, sour, and umami [98]. In a biological sense, gustatory cells identify stimuli by activating certain gustatory receptors,

which vary in structure according to the stimulus[99]. There are four different types of oral papillae, each responsible for different taste perceptions - sourness, saltiness, bitterness, sweetness, and savoury (also known as umami) [100]. When TRCs come into contact with various chemicals or ions, they can distinguish between various tastes: molecules that attach to G protein-coupled receptors on the cell membranes of taste buds cause them to taste sweet, savoury, or bitter. Alkali metals produce the taste of saltiness while hydrogen ions result in a sourness [93].

When the TRC is activated, peptides and neurotransmitters are released into the afferent fibre terminals of cranial nerves VII, IX, and X (facial, glossopharyngeal, and vagus nerves, respectively). In turn, they transmit information to the central nervous system, which is then sent to the thalamus and insula by way of the nucleus tractus solitarius, which is located in the brainstem [101]. The anterior insula and the frontal operculum are the components that make up the main gustatory cortex. Additionally, the insula is able to take in information from a variety of additional sensory modalities, including as pain, temperature, touch, and olfaction [102]. The pathways of identifying the taste attributes of food and regulating eating habits are classified into sensory, hedonic and physiological domains[103]. The sensory domain focuses on the identification, acknowledgment, and assessment of the magnitude of a stimulus, such as determining if a specific food has a sweet flavour and gauging its level of sweetness [104]. The detection threshold refers to the lowest concentration at which a participant can distinguish a taste stimulus from water, whereas the recognition threshold refers to the lowest concentration at which a person can identify the specific flavour quality of the stimulus [105]. The hedonic domain pertains to the motivational aspect of consuming a stimulus, such as the degree of desire for a specific food and the level of enjoyment experienced while eating it [106].

While the physiological domain encompasses the body's responses to sensory stimuli, such as the olfactory or visual perception of food. These interactions result in the activation of pathways that aid in digestion and the maintenance of homeostasis [107].

1.3.5.2 Types of papillae

Mammalian tongues contain four different varieties of papillae on their dorsal surface: fungiform, circumvallate, foliate, and filiform. The first three varieties contain tastebuds while filiform papillae, which are located on the front and back of the tongue, do not because their function is to make the surface of the tongue rough and thus aid in speaking, chewing and cleaning the mouth [100]. Fungiform papillae are mushroom-like structures, located on the side and back of the tongue and contain taste buds which play a crucial role in taste perception. Due to their relative sensitivity to a variety of systemic and local factors that affect the dorsum of the tongue, the quantity of these structures varies [108]. Foliate papillae are located on the sides at the back of the tongue, in front of the palatine-lingual arch of the pharynx [109].

The vallate papilla (also known as circumvallate), is the largest of the papillae and is located in a deep, continuous fissure on the caudal region of the dorsal surface. The quantity and shape of the vallate papillae differ greatly depending on the species [110]. The structures exhibit a range of sizes and shapes, encompassing round and flattened forms, and are positioned either in parallel or in rows along both sides of the caudal area. The inferior region of the vallate papillae harbours clusters of glands referred to as von Ebner glands. These glands are classified as salivary serous glands and possess ducts that discharge a clear fluid near the base of the grooves inside the papillae. This fluid aids in the dissolution of food and enhances the perception of flavours [111].

1.3.5.3 Basic Taste

The human tongue is capable of detecting five basic varieties of flavour: sweet, sour, salty, bitter and umami [93], Multiple signalling pathways are utilized by taste receptor cells to detect the chemicals in food. These cells are functionally categorized as follows: type I cells function as support cells and resemble glial cells; type II cells detect stimuli for bitter, sweet, and umami tastes; and type III cells detect stimuli for sour and salty tastes [112].

A sweet taste is caused by sugars (and substances that taste like sugar) such as Aldehydes and ketones which have a carbonyl group [113]. Taste buds contain several G protein-coupled receptors (GPCR) that are linked to the G protein identified as gustducin. The T1R2+3 (heterodimer) and T1R3 (homodimer) receptors enable the taste buds to sense a sweet taste [114]. The sweetest taste that can be detected is that of sucrose [115]. Taste sensitivity can be influenced by physiological factors (age and gender), pathologies (obesity and type 2 diabetes) and acquired behaviours (tobacco and alcohol use) [116].

Sourness is defined as an acidic taste and is measured via direct comparison with diluted hydrochloric acid, which has a sourness rating of 1 [117] and is detected by type III taste receptor cells which are distributed across all of the taste buds. Protons, which exist in great quantity in sour food, can enter the type III taste cells via proton channels [112]. The simplest receptor found in the mouth is the sodium chloride receptor which allows the tongue to sense saltiness produced by the presence of sodium ions; other ions of the alkali metals group will also taste salty [118]. The ability to taste bitter items has been linked to TAS2Rs (which are type 2 taste receptors - also known as T2Rs), particularly TAS2R38 in conjunction with the G protein gustducin [119].

The savoury taste, often identified as umami (of Japanese origin meaning good flavour or good taste), is viewed as an essential component of East Asian cuisine [120] and is produced by monosodium glutamate (MSG) which imparts an appetising flavour when paired with nucleotide-rich foods such as meat, fish, nuts, and mushrooms [121, 122]. Similar to how taste buds perceive sweetness through their reaction to sugar, savoury taste buds only respond to glutamate. Glutamate binding occurs at a distinct subtype of G protein-coupled glutamate receptors. L-glutamate possesses the capacity to interact with the metabotropic glutamate receptor (mGluR4), which belongs to the class of G-protein coupled receptors (GPCRs). This interaction leads to the activation of the G-protein complex, ultimately resulting in the perception of the umami taste sensation [123, 124].

1.3.5.4 Factors and Causes which Affect Taste Perception.

Many factors are capable of altering taste perception. Some people are born with issues affecting their sense of taste but, in most cases, they are predominantly caused by injury or illnesses such as infections of the middle ear and throat; radiotherapy treatment for head and neck cancer; exposure to specific substances (insecticides); exposure to certain drugs (antibiotics and antihistamines); ear, nose, throat surgery; and poor oral hygiene [125]. An additional factor is age: the production of saliva is reduced and the number of taste buds decreases [126, 127], although some studies have noted that the ability to sense sourness is less affected as a person ages [128, 129]. Smoking is also capable of affecting taste: the chemical compounds in the smoke come into contact with the taste buds and reduce their ability to distinguish the full range of tastes [130]. Obesity is another cause of a diminished sense of taste [131], with one study noting that the ability of obese respondents to correctly identify taste attributes was considerably worse than that of the control group (p 0.001). The ability to

distinguish salty, umami, and bitter flavours was dramatically diminished in obese people [132]. Some diseases such as cancer and anorexia reduce taste sensitivity [133, 134]. Patients following BS also experience taste change [135], the precise causes of the alteration in taste are not completely comprehended, there are various potential theories that might be considered; the surgical procedure modifies the biological composition of the taste buds, leading to a diminished capacity to perceive specific flavours [136]. Bariatric surgery may occasionally impair the vagus nerve which responsible for sending gustatory and olfactory information from the tongue to the brain [137]. The alteration in taste might be attributed to psychological reasons, such as an increased sensitivity to food following surgery due to reduced pleasure reactions to eating, which can be attributed to decreased activation in the brain's reward system [138]. Surgery results in decreased gastric acid secretion [139]. These acids are accountable for the decomposition of food and facilitating the body's assimilation of nutrients [140]. In the absence of these components, the process of food digestion becomes less effective, resulting in a decreased ability to absorb essential nutrients [141]. This can result in alterations in the gustatory perception of food [142]. Ultimately, those who have undergone bariatric surgery frequently see substantial weight loss. Weight reduction induces variations in hormone levels and other metabolic alterations that might impact taste perception [143]. Diabetes mellitus and depression can both lead to gustatory dysfunction specifically affecting the perception of sweetness [144]. In fact smoking also cause lower taste sensitivity [130].

1.3.5.5 Taste Dysfunction

Food and drink preferences are primarily motivated by taste and the ability to recognise and appreciate agreeable food and drink contributes to a person's physical well-being. Any alteration in taste perception, causing a persistent, unpleasant taste even when the mouth is

empty, is the most typical taste abnormality. Hypogeusia is a syndrome in which a person's capacity to sense umami, sweet, sour, bitter, salty, and other flavours is diminished [125]. Ageusia is the term for a condition where some people are diagnosed as 'taste blind' (although a complete loss of taste is uncommon); most frequently, patients report losing their sense of smell rather than their sense of taste [125]. Another condition, dysgeusia, produces a persistent unpleasant, salty, rancid, or metallic taste and is sometimes associated with burning mouth syndrome (a painful burning sensation in the mouth) which is prevalent among middle-aged and older women [145]**.**

Despite the prevalence of taste abnormalities, only a small number of therapies have been documented. Taste disorder treatments depend on the underlying cause of the illness and a general medical issue can frequently be resolved to restore flavour. Most reports of an alteration of taste function appear to be caused by the side effects of medications [146].

1.3.5.6 Impact of taste change in eating behaviours

Eating behaviour provides a more specific characterization of the eating process in humans since it incorporates the many mechanisms involved in the identification of appropriate times for consuming food and the recognition of situations in which eating is not advisable [147]. Eating behaviour also affects the quantity and composition of meals which is subject to several internal and external circumstances [148] such as alterations in taste perception, gastrointestinal movement, psychological discomfort, and physical discomfort, among other influences [149-151]. The perception of taste appears to have a significant role in regulating eating behaviour and dietary compliance specifically in terms of influencing food preferences, hunger, and calorie consumption. Several studies have documented post-operative alterations in subjective taste, smell, and food preferences, which have been associated with a potential reduction in long-term calorie intake [135]. Nevertheless, numerous mechanisms have been

proposed to elucidate the decline in the intake of high-caloric-density foods [152]. These mechanisms encompass malabsorption of nutrients [71], diminished gastric volume[153], adherence to postoperative nutritional guidance [154], modifications in meal size[155], alterations in gastro-intestinal signals (including hormones and incretins)[155], and shifts in taste perception and food preferences [156]. A recent review found that taste loss among elderly individuals has been observed to potentially result in reduced food intake or a preference for more intense flavours, the nutritional surveys have indicated an increased consumption of foods that are characterized by higher levels of sweetness and saltiness in this population [128]. In another study, the authors reported that the alteration of taste and smell among COVID-19 patients primarily results in diminished appetite, thereby causing a heightened sensation of satiety during meal consumption and consequently leading to a reduction in body weight [157]. Taste change among cancer patients was also found to be associated with loss of appetite and change in food preference [158]. Taste change and alteration of food behaviour have a positive impact on sustaining weight loss after bariatric surgery [159], in addition to a significant reduction in negative food habits among those population [160]. In contrast, taste alteration among AGB and RYGB were not associated with changes in taste sensitivity [159]. Despite the positive effect of taste alteration in reducing food intake and therefore weight reduction following bariatric surgery, this change may affect patients' general health and quality of life due to loss of food enjoyment and healthy food selection [161, 162]. The research on the psychological impact of taste change following bariatric surgery is limited and needs further investigation.

1.3.5.7 The Role of Saliva in Taste

Saliva production occurs within the oral cavity through the activity of three primary pairs of glands and several other minor salivary glands [163]. The parotid, submandibular, and

sublingual salivary glands are responsible for the production of around ninety per cent of the saliva, with the minor salivary glands accounting for the remaining ten per cent [164]. The total amount of saliva refers to the volume of saliva secreted by both the main and minor salivary glands. Submandibular glands create around two-thirds of the total volume of saliva in the resting (unstimulated) condition [165]. The parotid glands are accountable for a minimum of fifty per cent of the whole saliva volume generated by the oral cavity in reaction to stimulation. During both the unstimulated and stimulated stages of the salivary glands, the sublingual glands provide a minimal contribution [164]. The amount of saliva produced is dependent upon the type, duration, and intensity of substances in the mouth [166]. Strong acidic stimulation, high frequency of chewing, and strong biting force all result in increased saliva production [167]. Saliva is responsible for facilitating chewing, tasting and swallowing while, simultaneously, ensuring that the mouth remains moist and comfortable [168]. Saliva contains an insignificant percentage of protein and salt. The average daily saliva output ranges from 0.5 to 1.5 litres [164] and the unstimulated saliva flow rate is between 0.3 and 0.4 millilitres per minute. While sleeping, this rate is reduced to less than 0.1 ml/min and increases to 4.0-5.0 ml/min during eating, chewing, and other stimulating activities [169].

Saliva is the prime fluidic component of the external environment of taste receptor cells and, as such, it may contribute to taste sensitivity. Its primary function is to carry flavour chemicals to taste receptors. In the initial stages of taste perception, saliva functions as a solvent for flavour chemicals; salivary water dissolves taste molecules, which can then diffuse to taste receptor sites. During this process [170], saliva also protects the taste receptors from damage caused by dryness and bacterial infection that may be associated with taste abnormalities [171].

1.3.5.8 Connection between Saliva and Taste Buds

The chewing process breaks down food into smaller bits. Nevertheless, the physical act of mechanically reducing solid food into tiny particles [172] is not the only activity that

necessitates seamless operation. Saliva plays a crucial role in the oral cavity by facilitating the formation of a cohesive and malleable bolus, thereby facilitating the process of swallowing [173]. Additionally, saliva serves as a solvent that aids in the perception of taste by protecting taste receptors from damage and facilitates the transportation of taste stimuli to the receptor sites [170]. This elucidates the reason why individuals experiencing xerostomia commonly perceive altered or reduced gustatory sensations [174]. Xerostomia (a decrease in the production of saliva) could lead to taste disorders and can be instigated by many external factors such as antihistamines, decongestants, high blood pressure medication, antidiarrheal medication, muscle relaxants, urinary incontinence drugs, some Parkinson's disease medication and several antidepressants [65]. Other causes of dry mouth include age, cancer treatment, injury or surgery**,** and dehydration [175].

Certain bioactive constituents included in saliva aid in the generation of minuscule food particles, facilitating their interaction with taste receptor cells through the taste pores located within the taste buds [170]. This process is also effective when consuming soft or liquid meals that do not need mastication. After traversing the taste pore, the minute food particles proceed to activate the taste receptor cells located within the taste bud [93]. When taste receptor cells are activated, they transmit information related to flavour to the brain. Consequently, it is the brain that ultimately generates our sense and sensation of taste [176]. The taste receptor cells exhibit a high degree of specialisation, selectively detecting certain categories of fundamental flavours [176]. The salivary glands and taste buds exhibit an intricate interconnection since a substantial number of taste buds are situated within the grooves of the foliate and circumvallate papillae. These specific papillae host the lingual minor salivary glands, also known as von Ebner's glands, which are responsible for the secretion of saliva [170].

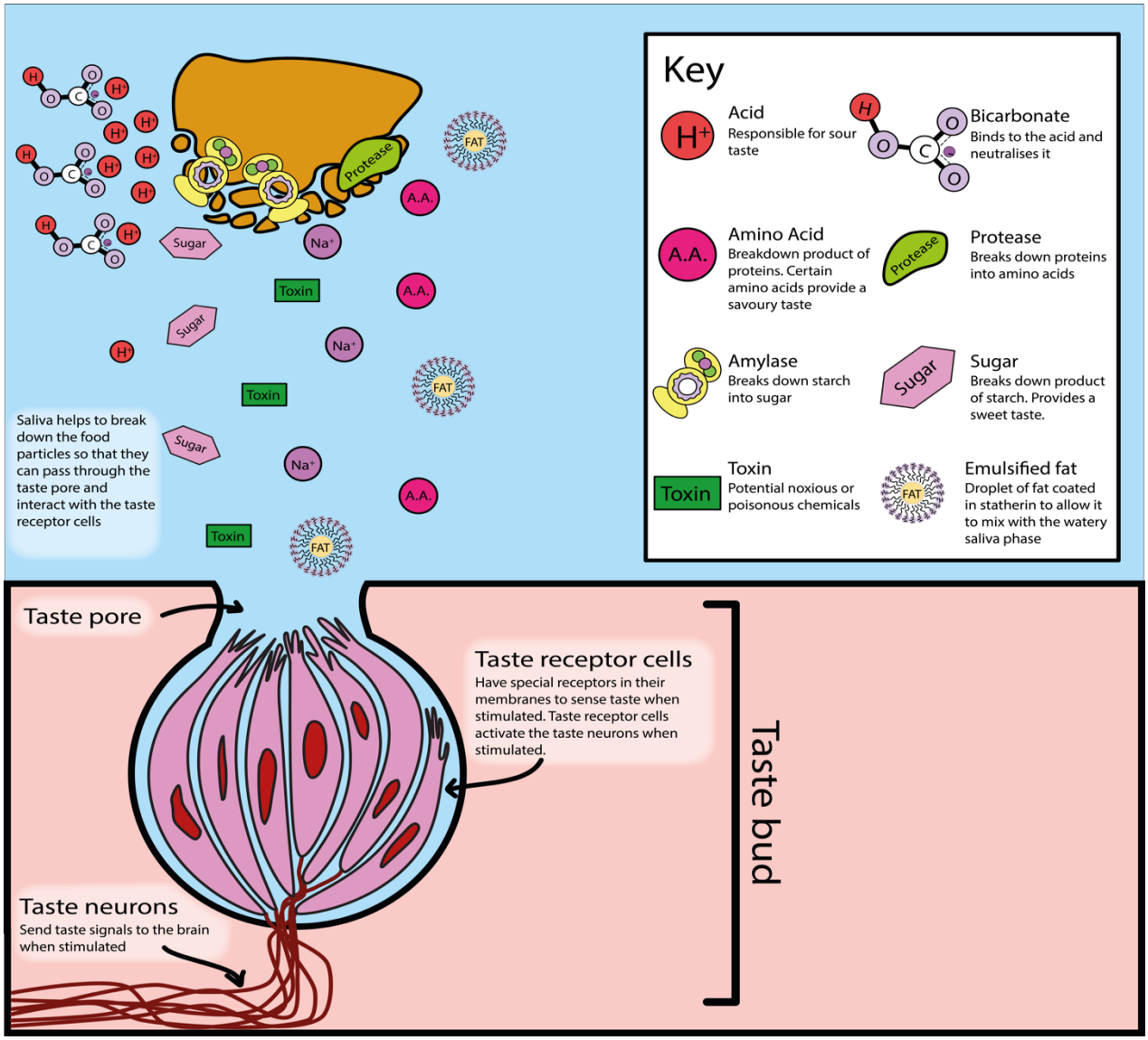


Figure 1.4 The role of saliva in the taste [177].

There are several distinct constituents and agents responsible for the enzymatic breakdown of food, facilitating its interaction with taste receptor cells located in the taste buds. The constituents present in saliva are responsible for the exposure of minuscule food particles to taste receptor cells. The little green symbol "Toxin" represents mostly bitter tastes [177].

1.3.6 Hair Loss Following Bariatric Surgery

Following bariatric surgery, many patients have reported experiencing hair loss although there is a lack of supporting data to corroborate this. However, current research has noted that hair loss does occur and can quantify their results: In a study conducted in 1996, it was observed that out of 130 patients who had undergone vertical gastrectomy (VG), 47 cases of hair loss were identified [113]. Similarly, another study documented 16 instances of hair loss among 42 patients who had undergone sleeve gastrectomy (SG) [114]. Furthermore, Coupaye et al. [178] reported 18 cases of hair loss among 43 patients who had undergone SG, and an additional 21 cases among 43 patients who had undergone gastric bypass (GB) six months post-surgery [178]. According to the findings of these studies, individuals who have had BS do experience hair loss, which lends credence to the anecdotal evidence provided to bariatric multidisciplinary teams (MDTs).

Hair loss was observed in certain patients who were advised to use vitamin and mineral supplements, while diligently adhering to the dietary and nutritional guidelines provided by their bariatric multidisciplinary teams (MDTs) [116]. To mitigate and reduce post-bariatric surgery hair loss, a considerable number of individuals sought guidance from their multidisciplinary teams (MDTs) as well as online forums and support groups specifically designed for bariatric patients. These sources provided valuable insights into supplementary hair treatments, which mostly involved the use of nutritional supplements and shampoos enriched with biotin, protein, zinc, or selenium. Furthermore, a considerable number of patients have used various forms of biotin supplementation for aesthetic purposes to preserve the vitality of their hair [117].

Throughout a typical hair cycle, the anagen phase, which denotes the growth phase, encompasses around 90% of the hair, while the telogen phase, also known as the telogen effluvium or hair loss phase, accounts for a mere 10%. Various factors might contribute to the exacerbation of telogen effluvium-related hair loss, including significant surgical procedures, hormonal fluctuations, deficiencies in iron or zinc, inadequate protein consumption, sudden weight loss, crash dieting, and the use of certain medications[179]. The psychological distress caused by hair loss can significantly affect an individual's overall well-being, despite the non-essential nature of hair for sustaining optimal health [118].

1.3.7 Weight Regains (WR) Following Bariatric Surgery

WR is defined as progressive weight gain that occurs following an initial weight reduction (measured as EWL > 50%) [180]. Successful weight management and the prevention of unintended weight gain from extra body fat are the most crucial elements following bariatric surgery. Regaining lost weight after surgery is a potential complication that might reduce the effectiveness of the treatment and necessitate further measures. Some post-surgery evidence has noted that some individuals report weight gain or inadequate weight reduction. A study of weight regain following BS revealed that 28.1% of patients acquired substantial weight over an average duration of 8.3 months and that food-related behaviour and work activities played a statistically significant role in weight recovery [181].

A recent systematic review indicated that weight regain rates following sleeve gastrectomy ranged from 5.7 % at 2 years to 75.6 % at 6 years. Initial sleeve size, sleeve dilatation, elevated ghrelin levels, insufficient follow-up assistance, and maladaptive lifestyle behaviours were all cited as possible reasons for weight return [182]. In a recent long-term study, 93% of patients

who had undergone RYGB surgery sustained at least a 10% weight reduction from baseline; 70% maintained at least a 20% weight loss; and only 40% maintained at least a 30% weight loss after 12 years [183-185]. This return appears to occur most often between 2 and 5 years following gastric bypass surgery. The type of surgery conducted, binge eating disorders, patient adherence to support groups, and presurgical BMI are all factors that contribute to weight maintenance or regain following surgery [186]. The expansion of the gastro-jejunal (GJ) stoma, following RYGB surgery, is also a contributing factor to weight regain: the surgery alters the speed at which the stomach pouch deposits its contents into the jejunum, resulting in a modification of incretin production and a decrease in satiety, enabling the patient to ingest more food each meal [187].

Patients who experience weight regain following BS often develop psychological effects including despondency, discouragement, embarrassment, and frustration. A recent study suggests that internal and environmental variables, such as psychological issues, changes in appetite, and physical and mental health concerns, may contribute to weight reduction. Social support, self-care, and behavioural measures may facilitate long-term weight control following surgery [188]. The management of weight regain following bariatric surgery is problematic and requires a multidisciplinary approach comprising general and plastic surgeons, dietitians, endocrinologists, gastroenterologists, psychologists, psychiatrists, and fitness trainers [189].

Several studies have suggested that a combination of behavioural interventions (such as cognitive behavioural therapy), pharmacotherapy, and lifestyle adjustments are effective at reducing weight regain and supporting weight loss outcomes [190]. Additionally, the employment of appetite suppressants and endoscopic interventions are effective at addressing weight regain caused by dilution of the GJ stoma following RYGB surgery [187]. Surgical revision may be performed after BS for a variety of reasons, such as the development of an

intractable marginal ulcer, gastro-gastric fistula, severe gastroesophageal reflux, or malnutrition [191].

1.3.8 Appetite modification following bariatric surgery

Every individual's eating behaviour is influenced by their appetite. Appetite is defined as the desire to eat food and is instigated by hunger. It exists in all higher life forms and serves to regulate proper energy intake to maintain metabolic demands. It is controlled by the digestive tract, adipose tissue, and the brain. [192]. There is no doubt that the initial weight loss after all types of bariatric surgeries is caused by decreased energy intake and macronutrient composition as patients who have bariatric surgery are advised to consume low-fat, low-energy-density foods during the first week following surgery and are given a liquid low-calorie diet, and following around 6 to 8 weeks depending on patients situation, patients start eating regular foods [193]. Evidence showed that RYGB patients reveal extremely considerable decreases in calorie intake (relative to pre-surgical levels) of around − 55% at 6 months and about 40% after 2 - 3 years. Energy intake (EI) for the earlier post-surgical period may be significantly lower, at around − 70% to − 80% [194, 195]. A recent systematic review and meta-analysis comparing the impact of GB and SG on dietary intake revealed that bariatric surgery significantly decreased energy intake by 1050.04 kcal/day ($p < 0.001$) compared to the baseline values of energy intake [196]. EI appears to be the primary factor in both weight reduction and the prevention of weight regain. Hormones most closely associated with feeling of hunger and satiety are ghrelin and leptin. The gut- brain axis controls appetite and satiety, ghrelin found throughout the gastrointestinal tract and is generated by the cells of the fundus of the stomach, the bulk of which are destroyed during a bariatric procedure [197-199].

Leptin is considered to be an opposing hormone to ghrelin. It is produced in the fat cells of the body when ghrelin levels are low and is responsible for the transfer of messages regarding

satiety (following eating) between the gut and the hypothalamus. The principal function of leptin is to regulate long-term energy balance - how many calories are consumed and burned and the amount of stored fat in the body [200]. Obese people display resistance against leptin signals to the brain which causes an increase in ghrelin production which increases a person's sensitivity to these cues, causing them to feel full after consuming reduced amounts of food. Postoperatively, patients report changes in appetite and nutritional consumption that may enable permanent weight maintenance [201]. Evidence showed a significant decrease in ghrelin production following BS which may associated with weight loss [202]. Research comparing RYGB and SG found that there was a considerable decrease in ghrelin levels after meals in the SG group, but no change in the RYGB group. The research found that a significant decrease in ghrelin levels after SG was linked to more effective hunger control and more weight loss in the first year following surgery compared to RYGB [199]. Resecting the fundus has a greater effect on ghrelin levels than just skipping it [203]. The absent of food intake control following bariatric surgery can lead to confused and crossed of satiety signals which cause stomach stretch and this can be permanent [204].

Most human studies reveal some malabsorption of nutrients following BS especially of fat [205]. The efficiency of fat absorption in one human research reduced dramatically following RYGB, from 92% before to surgery to 72% after 5 months and 68% at 14 months [206]. This translates into losses of 124 and 172 kcal/day. The study found that malabsorption was responsible for approximately 6% at five months and 11% at fourteen months of the overall decrease in metabolizable EI, based on parallel measures of EI. However, studies found little to no effect on malabsorption on weight loss following BS [205].

In summary, EI and metabolizable energy are drastically reduced at least initially and are mainly responsible for the weight loss phase [207]. It is unclear what processes lead to appetite

suppression, especially when significant weight loss is involved. While several post-operative changes in food preference[208], taste perception[209], hedonic assessment [210], motivation, and self-control [211] have been seen their significance and relative role in reducing appetite has not yet been established.

The underlying systems accountable for the lowering of weight and its subsequent maintenance after surgical intervention are intricate and little comprehended. In earlier studies, the prevailing notion was that weight loss mostly occurred through stomach restriction and impaired absorption of nutrients [132]. However, these physiological alterations do not fully account for the sustained effectiveness in maintaining body weight over the long term. The maintenance of weight is heavily influenced by appetite [133], which is controlled by many physiological mechanisms in the neuroendocrine system as well as sensory, cognitive, and physical processes that communicate feelings of hunger and satiety [134]. Over 25 years ago, Blundell introduced the satiety cascade, an important theoretical framework that outlines the many internal cues that alter feelings of satiety and satiation over time [212], summarized in *figure 1.5.* It can be evaluated via objective methods such as EI; subjective methods including Visual Analogue Scales (VAS); or biochemical methods such as measurements of circulating gut hormones. However, such methods continue to rely on subjective verbal input and would benefit from the addition of more direct objective metrics [213, 214].

Typically, appetite change following BS is related to circulating gut hormones and evidence has demonstrated that the postprandial PYY and GLP-1 responses are reduced in patients with poor weight loss following gastric bypass and with increased hunger compared to individuals with satisfactory weight loss. Inhibiting gut hormone responses, such as PYY and GLP-1, results in the restoration of hunger and an increase in food consumption. [214]. It is now firmly established that bariatric surgeries affect both hunger and metabolism. Following bariatric

surgery, the proposed mechanism of appetite is altered due to the removal of a section of the stomach; the nerves that conduct messages concerning hunger, craving and satiety between the gastrointestinal tract and the brain as part of the central nervous system are affected which impacts the sense of taste, sense of smell and satiety and decreases dietary intake [215].

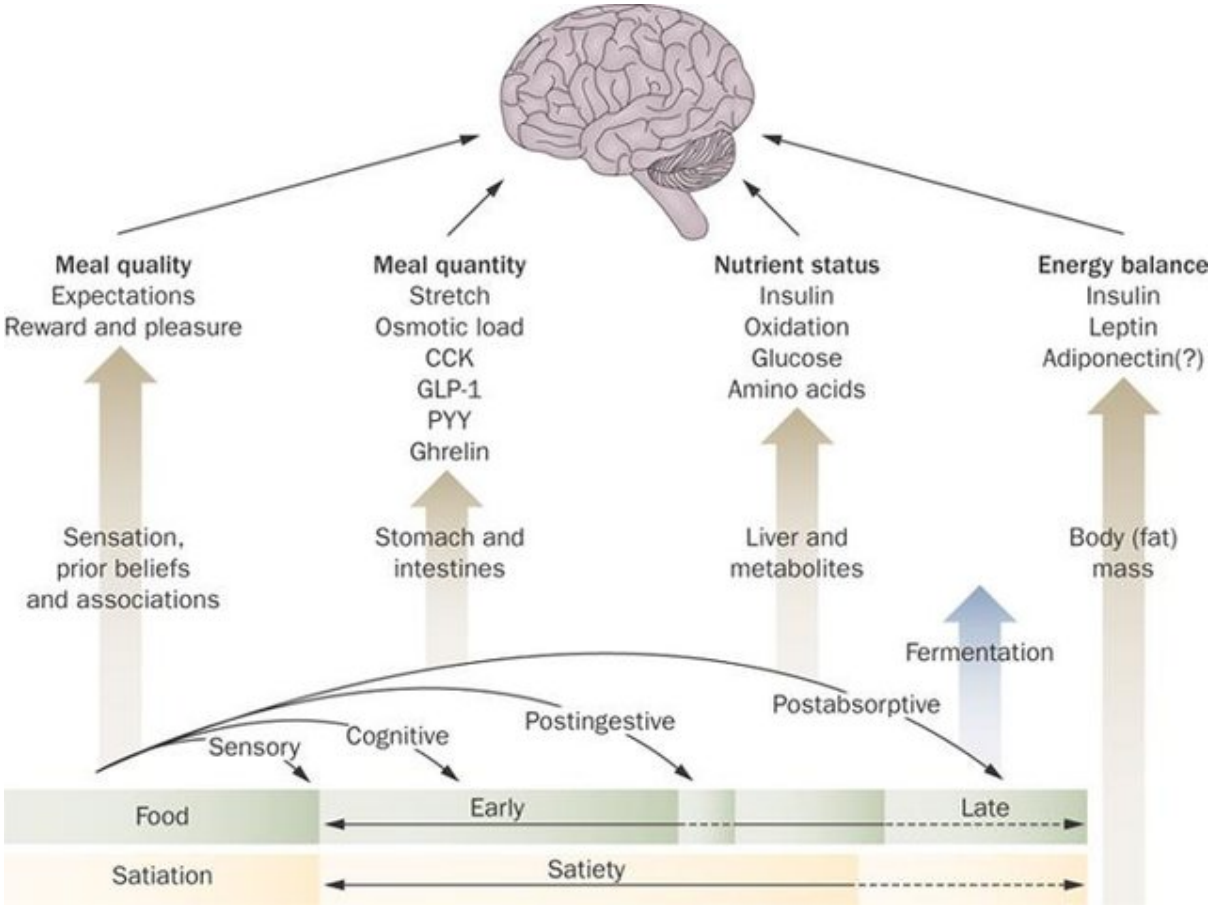


Figure 1.5 Summary of satiety cascade [216]

1.3.9 Dietary assessment methods for measuring food intake.

Dietary assessment methods are appropriate for various types of research and different groups of people. Various factors, including the research issue, study design, sample characteristics, and sample size, impact the choice of assessment technique[217]. There are four common dietary assessment methods for measuring food intake, include; food records, food frequency surveys, 24-hour recalls, and screening tools [218]. These evaluations allows for the

comprehension of the impact of diet on human health and illness, as well as the development of nutrition policy and dietary recommendations (such as specific foods and diet patterns) for individuals, groups, and communities [219].

1.3.9.1 The Food Record and 24-hour dietary recall (24HR)

Currently, national nutrition studies globally have utilised dietary record or 24-hour dietary recall methodologies [220]. A food record, often known as a food diary, is a self-reported log detailing all foods, drinks, and perhaps dietary supplements ingested by an individual over a period of one or more days. As the instrument is open-ended, there is an unlimited capacity for reporting things. Respondents are usually asked to document foods and drinks as they are eaten during the day in real-time. Completing the daily meal record requires a minimum of 15 minutes [221]. While the 24HR method depends on a skilled interviewer, a precise recollection of food consumption, the capacity to estimate portion sizes, and the interviewee's trustworthiness in providing correct information are important factors determining its reliability. This approach may be conducted by telephone, is appropriate for extensive surveys, and imposes minimal strain on responders [222]. These two dietary assessment methods have several limitations and advantages. The food record method is more precise for meals that are peculiar to a culture, distinct cuisines, or foods that are infrequently consumed. It also reduced the dependence and reliance on memory. The selection of foods or amounts may however be impacted by a relatively high responder burden and patients also tend to record less carefully the longer the session lasts. The advantages of 24HR includes the administration of food intake via telephone or in-person to both literate and illiterate populations. Because the later takes into account the previous day's consumption, individuals are less likely to change their eating habits. However the disadvantage of this method includes the dependence on a proficient interviewer, necessitates strong recall abilities, and can be influenced by unintentional or deliberate reporting inaccuracies, seasonal fluctuations, and day of the week [223].

1.3.9.2 Food-frequency Questionnaires (FFQ) and Screening Tools

Food Frequency Questionnaires (FFQ) is a tool used to gather dietary information by using a list of particular foods to estimate a person's typical diet and analyse how eating habits may impact health results[224]. However, this tool is less accurate when compared to dietary record or 24-hour dietary recall [225] because FFQs employ closed-ended techniques with a restricted selection of food and drink items, frequency of consumption options (e.g., 3–4 times/week, ≥2 times/day), and portion-size options (e.g., <0.5 cup, 0.5–1 cup, >1 cup). The limited selection of questions and response categories on a FFQ may also lead to measurement inaccuracies [225]. For the recording of a specific food habit of individuals however, FFQs may be more efficient and require less time to conduct compared to a 24-hour Dietary Recall, especially when the list of foods is concise (e.g. <100 items) [226].

When specific information is sought, such as dietary estimations of a particular nutrient (for example, calcium), food categories (for example, fruits and vegetables), or dietary fat, screening techniques are often used [227]. The Dietary Screening Tool evaluates food quality and classifies eating behaviours into different nutrition risk groups [228]. There are limits with screeners that are comparable to those discussed above for FFQs; however, screeners, by their very nature, only query a limited number of things simultaneously. The questionnaire inquiries about basic food-related information and usual eating habits, and may be completed and scored in about 10 minutes [229]. Nevertheless, if a specific topic is of interest, these tools provide a way that is both quick and cost-effective, and they often involve a little amount of hardship for the participants [230]. FFQs and screeners are similar in that they depend on general memory rather than specific memory, and it is possible that some demographic subgroups will find it simpler to complete them. Nutrition risk screening is a distinct category of screeners that is mostly used in clinical settings [218]. Moreover, research has shown that a body mass index

of less than thirty is linked to a notable underreporting of food intake [231, 232]. In contrast, a recent study found that people living with obesity do not tend to underreport their food consumption compared with people without obesity [233] .

1.4 Research Aims and Objectives

1.4.1 Rational

Currently, VLCD and bariatric surgery are viewed as effective treatments for obesity; however, long-term compliance has not been thoroughly investigated by the existing literature. BS is considered to be an effective long-term treatment; however, it may cause multiple side effects, including taste change, which may affect a patient's quality of life. Additionally, zinc deficiency following BS has been reported six months after surgery in many studies including by Dalcanale et al [234], Ruz et al. [235], and Pech et al. [236]. A systematic review of taste change following bariatric surgery revealed that taste change was reported six months post-operative [135].

The concurrent nature of these side effects suggests a potential correlation between zinc deficiency and taste change, although the specific role played by zinc in taste change following BS has not been analysed. In current clinical practice, patients receive between 8-15mg of zinc supplementation; however, current evidence has noted improvements in taste function among patients who have received a daily zinc supplement of 30-45 mg over six months [237]. These results suggest that current post-operative zinc supplementation is inadequate at reducing instances of taste change among patients.

1.4.2 Aim and Objectives

This research project aims to investigate the compliance with a VLCD and to examine the correlation between taste change and decreased circulating zinc level following bariatric

surgery, the latter may also play a role in eating behaviour compliance post bariatric surgery. To address this aim, the research was divided into two sections. The first part includes:

1. A systematic review design to determine a potential relationship between zinc and taste - with or without BS. Many studies have discussed and proven taste changes following BS, however, none have analysed the causes and factors influencing taste change following BS. Since taste change and zinc deficiency frequently occur at the same time, this study hypothesises the presence of a relationship between these two factors.

2. A systematic review and meta-analysis of randomized control trials (RCT) regarding the effectiveness of zinc supplementation in taste disorder treatment. The systematic review implies evidence-based results regarding the positive effect of zinc in taste change treatment for various diseases. Therefore, this study hypothesises that an effective dose of zinc may be successful in avoiding taste change.

3. Recent studies have provided evidence concerning the prevalence of taste change and zinc deficiency following bariatric surgery. A considerable number of RCTs have demonstrated the effectiveness of zinc supplementation among subjects with a zinc deficiency, those with idiopathic taste disorders, and patients with taste disorders induced by chronic renal failure (when given in high doses ranging from 68 to 86.7 mg/d for up to six months); however, any association between zinc deficiency and taste change following BS is inadequately understood. The findings of the systematic review will inform this study and allow for an examination of the potential correlation between decreased circulating zinc and taste change via clinical study. Additionally, it will allow for an exploration of other side effects such as reduced salivary flow and hair loss.

4. The second component of the research project concerns an exploration of patient compliance with VLCD.

1.4.3 Outline of the Thesis

The outline of this PhD thesis is summarised in Figure 1.5.

Chapter 1 provides an overview of obesity; its current treatment paradigm (including risks and complications), with a focus on Bariatric Surgery and VLCD, overview of mechanisms and regulation of taste, common methodologies for the assessment of dietary intake; an outline of the aims (including research objectives), and the thesis structure.

Chapter 2 is a systematic review containing collated evidence regarding zinc deficiency and taste change following bariatric surgery to investigate any correlation between the two. This will be undertaken by discussing evidence regarding the association between taste change and BS; the connection between zinc deficiency and BS; and evidence relating to zinc supplementation on taste perception in general, and specifically concerning BS. The findings of this review will facilitate the design of the clinical study intended to evaluate the association between zinc and taste change following bariatric surgery.

Chapter 3 concerns details of the design of the clinical studies informed by the findings of the systematic reviews in chapter two which examined the association between taste change, hair loss, salivary flow rate and zinc deficiency.

Chapter 4a explores the correlation between zinc levels, taste change and salivary flow rates. A prospective cohort study was conducted and utilised data from forty-three patients who have undergone two types of bariatric surgery.

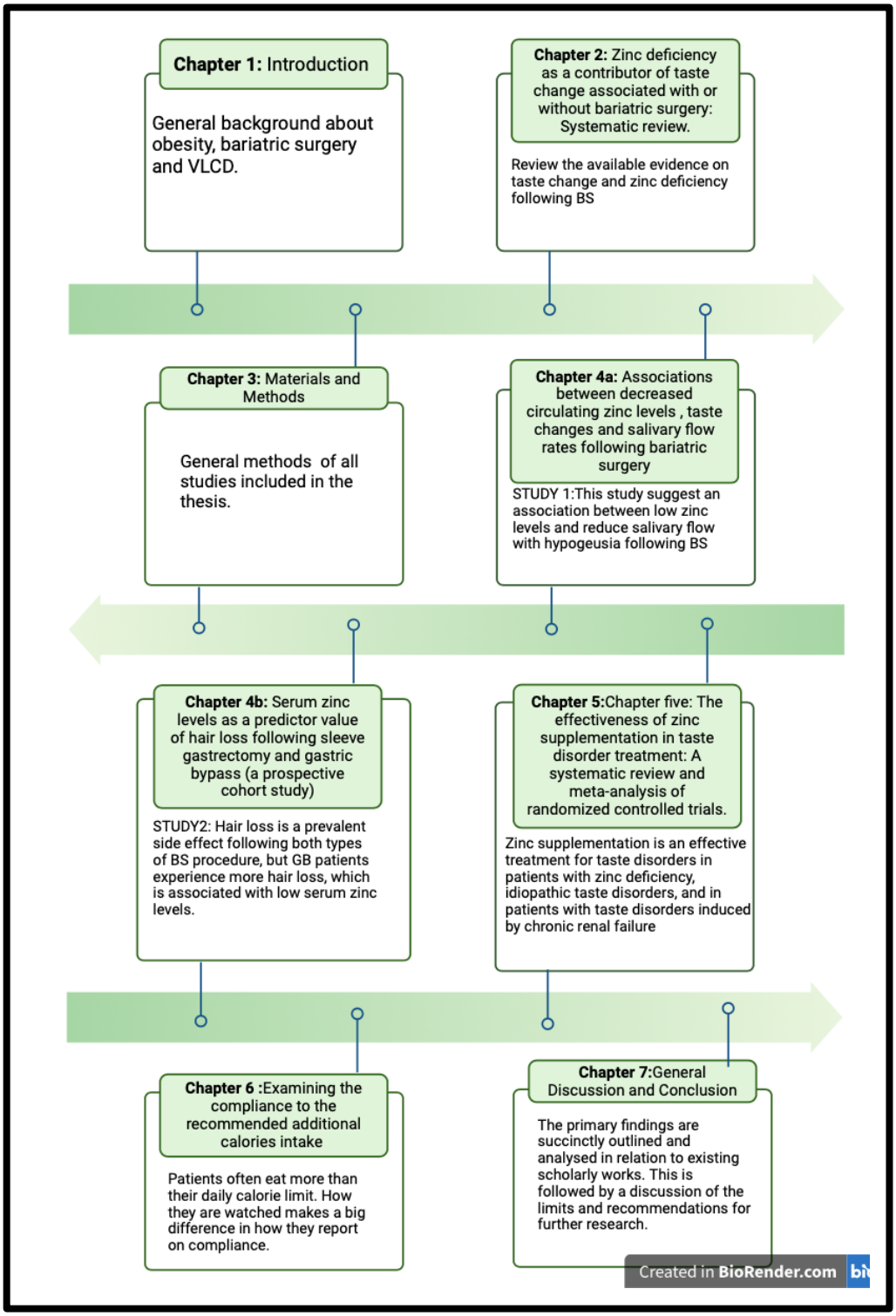
Chapter 4b examines the relationship between decreased circulating zinc levels and hair loss. For this study, a prospective cohort study was performed utilising data from forty-three patients who have undergone the two types of bariatric surgery.

Chapter 5 contains a systematic review and meta-analysis of randomized controlled trials designed to examine the effectiveness of zinc supplementation in taste disorder treatment and is informed by the findings from Chapter Two.

Chapter 6 contains an examination of patient compliance with a very low-calorie diet. The present study had a sample of 35 male participants who were healthy and of middle age. These individuals underwent a weight reduction intervention using a very low-calorie diet (VLCD), where meal replacement items were provided to supply a daily intake of 600 kcal. Additionally, participants were permitted to ingest an additional 200 kcal/day in conjunction with the VLCD.

In Chapter 7, conclusions from the previous chapters are discussed in detail. The main findings are outlined and examined in relation to the body of prior research. Additionally, it contains a discussion of the constraints of this study alongside the implications for future research concerning taste change and zinc treatment among bariatric patients.

Figure 1.6 Summary of thesis outline.



Chapter 2: Zinc Deficiency as a Contributor of Taste Change Associated with or without Bariatric Surgery: Systematic Review

Chapter Overview

This chapter reviews all available studies on taste change following bariatric surgery, zinc deficiency following bariatric surgery and all studies on the effect of zinc supplements on taste disorder treatment. The findings are then used to inform the research gap and subsequent studies in this thesis, it also informs the design of the clinical study to examine the association between zinc and taste change following BS. The findings of this chapter has been published in *Obesity Surgery Journal* entitled "A Literature Review of Taste Change and Zinc Deficiency After Bariatric Surgery: Could There Be a Causal Link?

2.1 Abstract

Background: Taste change or taste disorder is a frequent complication of bariatric surgery (BS) but can also be a consequence of many diseases. Many studies have found zinc deficiency to be associated with taste disorders. This review aims to investigate the role of zinc in taste change, and whether it is associated with bariatric surgery.

Methods: Data were extracted from existing studies and analysed according to specific inclusion criteria. A literature search was also conducted, using four electronic bibliographical databases—EMBASE, PubMed, AMED and MEDLINE. The search used the following keywords and terms: taste change; taste disorder; bariatric surgery; zinc, zinc sulphate or Zn; deficiency; supplementation, and micronutrient deficiencies. There were no restrictions on publication date, to facilitate the collection and identification of all available and relevant articles published before 30 February 2020.

Results: In total, 33 studies met the inclusion criteria. The total number of participants analysed was N= 3264. The results of this review were divided into three categories – 1) the effects of BS on taste, 2) the effects of BS on zinc levels and 3) the effects of zinc replacement on taste. Qualitative studies into taste change following BS using surveys reported that taste change occurred in most patients within 12 months of BS, but experimental studies did not find a significant change. Twelve studies investigating zinc deficiency following BS showed a significant decrease in zinc levels, six months after surgery. Supplementation with 45–50 mg of zinc sulphate was effective in improving taste, except in cancer patients, who showed no improvement in taste following zinc supplementation.

Conclusion: Zinc deficiency appears to be associated with taste change after bariatric surgery. Supplementation with much higher levels of zinc, at 45–50 mg, was effective in taste change treatment for many cases of taste disorder. Yet the routine levels of multivitamin and mineral

supplementation, currently prescribed to patients following BS, were not effective for avoiding zinc deficiency after BS—and were thus not effective for averting taste change. It is therefore suggested that taste change following BS may be related to zinc deficiency induced by the surgery.

2.2 BACKGROUND

Taste is an important sense—one linked with maintaining good health and quality of life. Taste change or taste disorder is a frequent complication, reported by numerous people following bariatric surgery (BS) or because of many other diseases. Around 200,000 patients visit doctors each year in the USA, complaining of either a taste or smell change [238]. In 2003, about 240,000 patients were diagnosed with taste disorders in Japan [239]. There are many causes of taste change—such as radiation therapy for cancers of the head and neck; surgery to the nose, ear and/or throat; antibiotics and some antihistamines; and exposure to some chemicals [238]. Bariatric surgery (BS) has emerged as the most cost-effective treatment to help obese patients lose weight [240]. Patients with BMIs of ≥35 kg/m^2 or ≥40 kg/m^2, as well as comorbidities—are eligible for the procedure in the UK. Over recent decades, the incidence of BS has increased globally. An estimated 468,609 surgeries were performed in 2013, according to a survey by the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)[241]. In the UK, about two-thirds of all hospital admissions in 2016 and 2017 were due to patient obesity; most of these patients were females. A total of 6,760 consultant sessions for BS were completed between 2016 and 2017 [242]. The most common BS procedure worldwide is the Roux-en-Y gastric bypass (RYGB), accounting for approximately 45% of all BS procedures. Sleeve gastrectomy (SG) represents 37% and adjustable gastric banding (AGB) comprises 10% of all BS procedures [241]. BS can lead to nutritional deficiencies, as well as to side effects such as dumping syndrome and gastroesophageal reflux [243]. Taste change is another

common important side effect reported by patients after BS affecting 73% of patients who underwent Roux-en-Y gastric bypass. However, evidence regarding the mechanism of taste change and the role of nutritional deficiency in mediating this effect is unclear. Increasing evidence highlights the importance of zinc for many body functions. Zinc deficiency can cause many clinical diseases found to be associated with taste disorders, as well as various other complications such as hair loss, poor appetite, and delayed wound healing [244]. As noted, zinc deficiency and taste change are both complications frequently reported after BS. A study reported that 40.5% of patients had zinc deficiency after gastric bypass, which was significant ($p = 0.008$) while Pech et al [236] found that 13.4% of participants had zinc deficiency after sleeve gastrectomy [236]. The British Obesity and Metabolic Surgery Society (BOMSS) guidelines recommend a complete multivitamin and mineral supplement (containing iron, selenium, zinc, and copper) after all types of bariatric surgery, to prevent micronutrient deficiencies (BOMSS, 2014) BOMSS recommends that multivitamin and mineral supplements should contain a sufficient amount of both zinc and copper [73]. Two mg of copper is recommended, and a ratio of 8–15 mg of zinc for each 2mg of copper should be maintained if an additional amount of zinc is required. Patients who undergo GBP require additional zinc and copper supplementation; specifically, 2 mg of copper and 15 mg of zinc per day [73]. The mechanism of taste changes following BS remains poorly understood. However, evidence shows that zinc deficiency causes changes in the levels of gustin concentration. Gustin is the major zinc-containing protein in the human parotid; low levels of Gustin have been linked with growth and development disturbances of the taste buds [245]. Therefore, decreased taste acuity may be due to low levels of total parotid saliva zinc. In one experiment on rats, for instance, the authors found that zinc deficiency induces the degeneration of soft palate taste buds, according to microscopy observations [246].

2.2.1 Aim and Rational

Many studies have discussed and proven taste changes following BS. However, none have discussed the causes and factors influencing taste change following BS. Since taste change and zinc deficiency frequently occur at the same time, we hypothesize a possible relationship between these two factors. Thus, this review aims to discover a possible relationship between zinc and taste—with or without BS.

2.3 Methods

2.3.1 Identifying relevant studies (Literature search)

A literature search was conducted, using the four electronic bibliographical databases of EMBASE, PubMed, AMED and MEDLINE. Article bibliographies were also searched and yielded additional relevant studies. The following keywords were used: taste change, taste disorder, disguise, bariatric surgery, bariatric surgery, sleeve gastrectomy, gastric bypass, banding and duodenal switch, biliopancreatic diversion, zinc, zinc sulphate or Zn, deficiency, supplementation, micronutrient deficiencies, vitamin and mineral supplementation and nutritional deficiencies. Appendix 1 outlines the full search method, using these keywords, *see Appendix 2*. There were no restrictions on publication date, to facilitate the collection and identification of all available and relevant articles published before 30 February 2020.

2.3.2 Selecting relevant studies

After duplicates and irrelevant articles were removed, the literature search produced 690 articles. Of these, 523 articles were eliminated due to their irrelevance to the research question after the title and abstract were screened. The other 175 articles were assessed for eligibility, and the full texts were reviewed to determine which sources fulfilled the inclusion criteria**.**

2.3.2.1 The inclusion criteria were

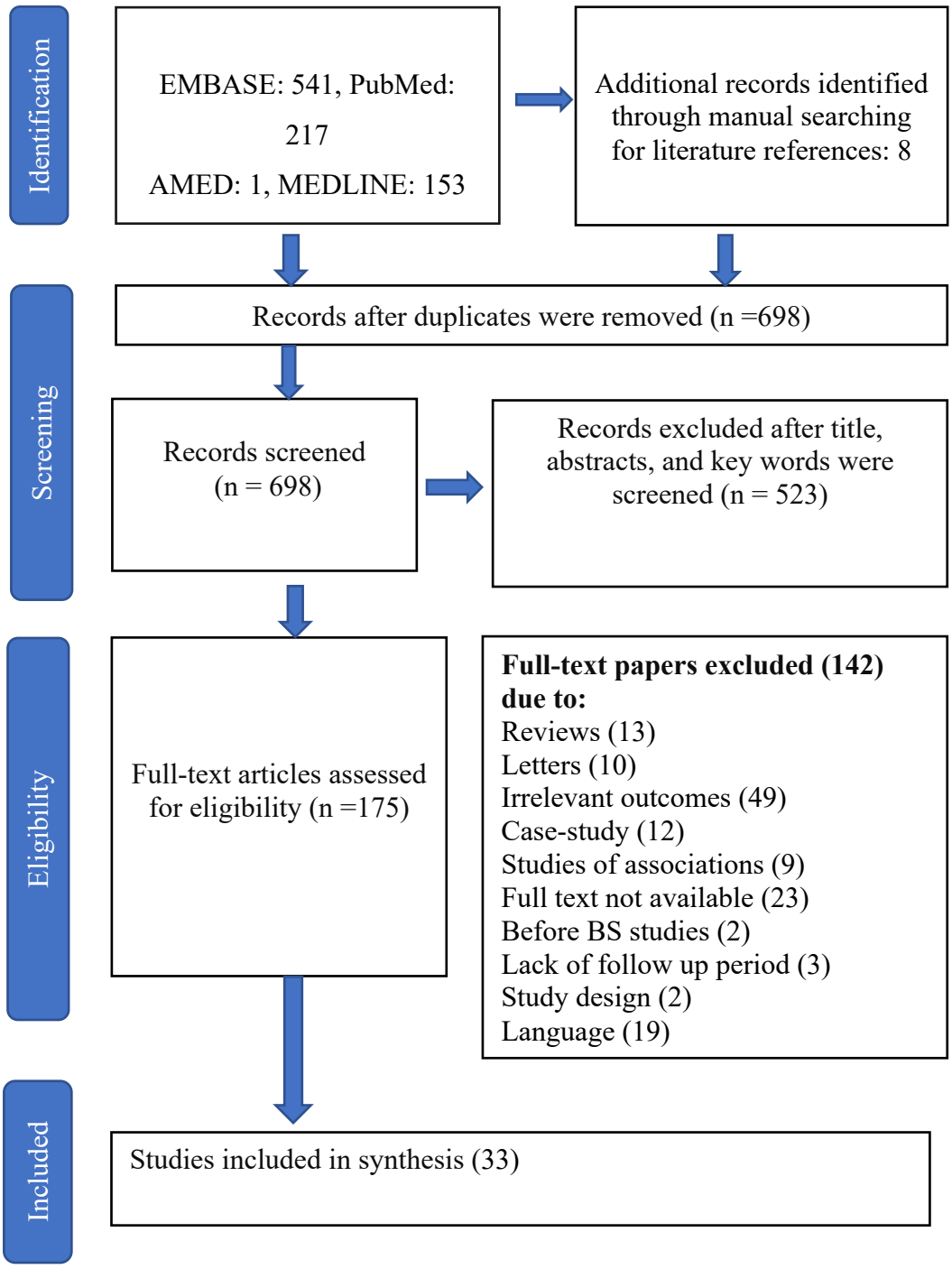
1. Randomised controlled trials (RCTs) and cohort studies.
2. Studies that focussed on zinc deficiency and/or taste change after BS (such as SG, GBP, banding, duodenal switch, biliopancreatic diversion, or gastroplasty).
3. Studies populations consisting of adults ≥18 years.
4. Studies regarding taste changes and zinc outcomes.
5. Articles in the English language.
6. Human studies.

2.3.2.2 The exclusion criteria were

1. Study populations ≤17 years.
2. Studies for which the full text was unavailable.
3. Studies that did not include zinc or taste change outcomes.
4. Studies not in the English Language
5. Cross-sectional studies and case-control studies.
6. Animal studies.

Thirty-three papers were found to fulfil the inclusion criteria (Figure 2.1).

Figure 2.1 Flow diagram demonstrating the article selection process.



2.3.3 Data extraction

The included studies were assessed and extracted, depending on three aspects. Table 2.3 describes studies about taste change following bariatric surgery and classified according to the author(s), year of publication, study location, study design and duration, population, type of BS, time since surgery, method, and taste change outcomes. Table 2.4 describes studies about zinc deficiency following bariatric surgery—which are classified according to the author(s), year and country, study design and duration, sample size and age, type of BS intervention and period, weight reduction science surgery, zinc dose, percentage of zinc absorption, and effectiveness of zinc supplementation. Table 2.5 describes the studies of the effectiveness of zinc in taste disorders. This table is classified into author(s), year and country, study design and duration, sample size, age, disease or case, methods, zinc dose/d, and treatment period.
Only one study was found regarding the role of zinc in taste change following BS [247], during data extraction. Meanwhile, many studies were found related to the effectiveness of zinc in taste change treatment. Because of the heterogeneity of the outcomes and methods, it is difficult to produce a meta-analysis. Thus, we have provided a narrative synthesis.

2.4 Results

The thirty-three studies that were analysed in this review are identified in tables 2.3, 2.4, and 2.5. Table 2.3 summarises the studies' demographic details—as well as the methods used to examine taste change following BS and the main outcomes of taste change following BS. Table 2.4 considers zinc deficiency and the effectiveness of routine multivitamin and mineral supplementation, following BS. Table 2.5 summarises all available RCTs that examine the role of zinc in taste change treatment, in patients without bariatric surgery. Owing to the

heterogeneous nature of the existing data, this review covers each of these domains, with data analysis provided for each section accordingly.

2.4.1 Study design

All 8 studies that examined taste change following BS, as presented in table 2.3, were cohort studies. Twelve RCTs and cohort studies investigated zinc deficiency following BS. These are shown in table 2.4. Thirteen studies investigated the effectiveness of zinc supplementation in taste change treatment in patients without BS, *table 2.5*. These studies were all randomized controlled trials, which are the gold standard study designed to examine the effectiveness of zinc in taste change treatment.

2.4.2 Participants' characteristics

The total number of participants analyzed was n= 3264, all participants in tables 2.3 and 2.4 had undergone bariatric surgery. Females comprised the majority of participants in all studies, except one study Pech et al. [236], where the number of males was higher. In Billeter et al.'s [248] study, the number of males and females were equal. Madan et al. [249] and Pires et al. [250] did not report the gender numbers in their studies. Participants' ages ranged from 18 to 70 years old.

None of the participants in table 2.5 had undergone BS. Five studies examined cancer patients [251-255], two studies investigated idiopathic taste disorders [256, 257]. One study [258] covered uremic hypogeusia. Two studied taste disorders in the elderly [259, 260]. Three studies dealt with taste dysfunction [261-263]. In all these studies, the number of participants for each gender was nearly equal, the age range was from 18 to 87 years old.

2.4.3 Quality assessment

The quality of the papers included was evaluated, using the Newcastle-Ottawa scale for randomized control trials and cohort studies. The quality assessment for the randomized controlled trial comprised three categories ('selection' contains four questions, 'comparability' contains one question, and 'exposure' contains three questions). The quality assessment for the cohort studies also included three categories ('selection' contains four questions, 'comparability' contains one question, and 'outcome' contains three questions). Each study can be given a maximum of one star for each numbered item within the categories. A maximum of two stars can be given for comparability. Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor) are the following: good quality 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. Fair quality 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. Poor quality 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

2.4.3.1 Randomized controlled trial (RCT) studies' quality assessment

Twelve studies were deemed to be of good quality [237, 252-256, 262-267], three studies were of fair quality [259, 268, 269]. *See table 2.1.*

2.4.3.2 Cohort studies' quality assessment

Nine studies were of good quality [236, 270-277]. Eight studies were of fair quality [234, 278-284]. One study was poor quality [247]. *See table 2.2.*

Table 2.1 Quality assessment for 15 randomized controlled trials

Author	Selection				Comparability		Exposure			Total
	Case definition	Representativeness of case	Selection of controls	Definition of controls	Main Factors	Addition-al factors	Ascertainment of exposure	Same method for cases and controls	Non-response rate	
Khan [254]	*	*	*	*	*	*	*	*	0	8
Najafizade, Hemati [253]	*	*	*	*	*	0	*	*	0	7
Lyckholm [252]	*	*	*	*	*	*	*	*	0	8
Rojas, Carrasco [269]	*	*	0	0	*	*	*	*	0	6
Ruz, Carrasco [268]	*	*	0	0	*	*	*	*	0	6
Sakagami [267]	*	*	*	*	*	*	*	*	0	8
Ikeda [259]	*	*	0	0	*	*	*	0	0	5
Stewart-Knox, Simpson [237]	*	0	*	*	*	0	*	*	0	6
Halyard, Jatoi [265]	*	*	*	*	*	*	*	*	*	9
Heckmann, Hujoel [262]	*	*	*	*	*	*	*	*	0	8
Sakai [256]	*	*	*	*	*	0	*	*	0	7
Ripamonti [255]	*	*	*	*	*	*	*	*	0	8
Mahajan, Prasad [266]	*	*	*	*	*	0	*	*	0	7
Atkin-Thor, Goddard [264]	*	*	*	*	*	*	*	*	0	8
Henkin, Schecter [263]	*	*	*	*	*	*	*	*	0	8

Table 2. 2 Quality assessment for 18 cohort studies

Author	Selection				Comparability		Outcome			Total
	Expos-ed cohort	Non-expos-ed cohort	Ascertain-ment of exposure	Out-come of interest not present at start	Main Factors	Addition-al factors	Assess-ment of outcome	Follow up long enough*	Ade-quacy of follow up	
Katsogridaki, Tzovaras [274]	*	*	*	0	*	*	0	0	*	6
Nance, Eagon [275]	*	*	*	0	*	*	*	*	*	8
Gero, Dib [277]	*	*	*	0	*	0	*	*	*	7
El Labban, Safadi [278]	*	0	*	0	*	*	*	*	*	7
Zerrweck, Zurita [279]	*	0	*	0	*	*	*	*	*	7
Billeter, Probst [276]	*	0	*	*	*	*	*	*	*	8
Papamargaritis [270]	*	0	*	*	*	*	*	*	*	8
Wang, [271]	*	*	*	0	*	0	*	*	*	7
Graham, Murty [280]	*	0	*	0	*	0	*	*	*	6
Gobato, Seixas Chaves [272]	*	0	*	*	*	0	*	*	0	6
Balsa [281]	*	0	*	0	*	*	*	*	*	7
Salle [283]	*	0	*	0	*	*	*	*	*	7
Madan, Orth [284]	*	0	*	0	0	0	*	*	*	5
Burge, Schaumburg [247]	*	0	0	0	0	*	*	0	0	3
Dalcanale, Oliveira [234]	*	0	*	0	*	*	*	*	*	7
Pech, Meyer [236]	*	0	*	*	*	*	*	*	*	8
Pires, Martins [273]	*	0	*	*	*	0	*	*	0	6
Tichansky, [282]	*	0	*	0	0	0	*	0	0	3

2.4.4 Association between Bariatric surgery with taste change: Qualitative studies

In a sample of 103 patients who underwent RYGB, 75% reported taste changes in a period of less than 12 months and that the foods that most commonly tasted different were meat (33%) and sweet flavours [280]. In a comparison between BS procedures, authors found that 35.5% of RYGB and 34% of SG patients reported a taste change in commonly consumed food, in a mean time of 10±6.7 months after surgery [279]. While there was no significant difference between the two surgeries in terms of taste change, patients presenting with food aversion experienced higher %EWL compared with those without aversion, (73.3±19.7 vs 65.8±19.4%; p= 0.046) [279]. In a further study, a comparison between RYGB and AGB in a sample of 127 patients, of whom 82 underwent RYGB and 28 underwent AGB. Decreased intensity of taste was reported in 82% of RYGB patients and 46% of AGB patients; ($p< 0.05$), 83% of RYGB patients and 69% of AGB patients agreed that loss of taste led to better weight loss [282]. A recent study of 100 patients who underwent SG found a decrease in preferences for core tastes, 6 months after surgery ($p < 0.002$), in this study the decrease in preferences did not influence significantly the % of total body weight loss except for salty taste a higher decrease in salty preferences correlated with a higher % of total body weight loss ($p=0.02$) [277]. In all four included studies that used questionnaires, the most important decline in taste preference was observed for sweet food [277, 279, 280, 282]. **(Table 2.3).** It is also conceivable that change in taste preference after bariatric surgery may be due to taste/food aversion due to dumping syndrome, but this is not explored.

2.4.5 Association between bariatric surgery with changes in sensory-discriminative component: quantitative studies

The evaluation of taste perception includes assessment of taste quality (sweet, salty, bitter, sour, umami) and taste sensitivity. The four included studies measured detection thresholds (the minimum concentration a subject must taste, to identify a taste stimulus as being different from water) or recognition thresholds (the minimum concentration that a subject needs, to recognize the taste quality of the stimulus). Burge, Schaumburg [247] found an increase in sweet taste sensitivity (decreased thresholds for sucrose detection and recognition) at 6 weeks post RYGB ($P<0.05$). In contrast, Nance, Eagon [275] found no change in taste sensitivity after one year of SG and RYGB $p>0.05$. El Labban, Safadi [278] did not find a significant change in sweet sensitivity ($P >0.05$) but did find a significant change in sourness thresholds, among subjects who had undergone RYGB $P=0.0045$. In a pilot functional magnetic resonance imaging (fMRI) study, the authors examined taste testing and fMRI for 13 subjects pre and post-BS and compared to controls in response to sweet and salty solutions, the author found a significant decrease in brain activation in the reward system responding to all sweet tastes compared to pre-surgery, however same effect appears in non-surgical controls ($p< 0.001$)[271]. In contrast, a significant increase in brain activation in the reward system responding to salty tastes after surgery compared to controls [271].

Table 2.3 Taste change following BS.

Author(s), year, and country	Study design and duration	Population	Type of BS	Time since surgery	Methods	Taste change outcomes	Food tasting differently
Burge, Schaumburg [247] Ohio	Prospective cohort; 12 weeks	*n* = 14 subjects (6 M, 8 F) Age = 38.4 ± 6 years	RYGB	6 and 12 weeks	Recognition thresholds Zinc level	Recognition thresholds for sucrose decreased significantly ($p < .05$) by 6 weeks after surgery and remained so at 12 weeks Correlation coefficients($r = .054$) indicate no relation between taste acuity and serum zinc level	Meat, sweet taste
Zerrweck, Zurita [285] Mexico	Prospective cohort; 6 MO	*n* = 154 patients (104 LGBP/50 LSG) all females Age: 30–55 years	RYGB, SG	10 ± 6.7 MO	Taste change Survey	Increased intensity of taste, 35.5% RYGB reported taste change 34% after LSG reported taste change, *p* value = 1	Fatty food and sweet taste
Wang [271], USA	Cohort; 1 year	*n* = 13 patients (5 M and 8 F) Age: 29–60 years	RYGB	1-month and 1-year post-surgery	fMRI and recognition thresholds	After surgery, brain activation responding to sweet tastes was significantly decreased in the reward system $p < 0.001$	Sweet taste
El Labban, Safadi [278] Lebanon	Retrospective cohort study; 6 months	*n* = 21 subjects (9 M and 12 F) Age: 19–50 years	RYGB or SG	6 MO	Sweetness acceptability test and recognition thresholds	There was no significant change in sweet sensitivity $p > 0.05$, but significant change in sourness thresholds among subjects undergoing RYGB $p = 0.0045$	Sour taste
Graham, Murty [280] Leicester, UK	Prospective cohort; 2000–2011	n = 103 patients (14 M and 89 F) Age: 25–63 years	RYGB	< 12 MO	Taste change Survey	Decreased intensity of taste; 75% reported taste changes	Meat (33%) and sweet taste

Author(s), year, and country	Study design and duration	Population	Type of BS	Time since surgery	Methods	Taste change outcomes	Food tasting differently
Tichansky [282], California	Cohort	*n* = 127 patients; 82 LRYGB/28 LAGB	RYGB, LAGB	> 1MO	Taste change Survey	Decreased intensity of taste ($p < .05$) in 82% LRYGB patients and 46% LAGB patients ($p < .001$)	Sweet food and meat
Nance, Eagon [275] USA	Cohort	*n* = 31 subjects RYGB (*n* = 23)/SG (*n* = 8) Age: 26–53	RYGB, SG	NR	Detection thresholds, suprathreshold	There was no significant effect of BS on taste change $p > 0.05$	No change
Gero, Dib [277] USA[1]	Prospective longitudinal observational study; 2014–2015	*n* = 100 consecutive LSG patients(77 F and 23 M) Age: 40.8 ± 12 years	LSG	6 MO	Taste change Survey	Taste preferences for bitter, salty, umami, fatty, sour, spicy, and sweet decreased significantly from baseline to post-surgery month 6 ($p < 0.002$)	Sweet food

1. Summary of 8 studies
2. [1]*n*, number; *SD*, standard deviation; *M*, male; *F*, female; *MO*, month; *NR*, not reported; *LGBP*, laparoscopic gastric bypass; *LSG*, laparoscopic sleeve gastrectomy; *LRYGB*, laparoscopic Roux-en-Y gastric bypass; *LAGB*, laparoscopic adjustable gastric banding; *RYGB*, Roux-en-Y gastric bypass; *SG*, sleeve gastrectomy

2.4.6 Association between bariatric surgery with zinc deficiency

Twelve studies have investigated zinc status following BS. A randomized controlled trial of zinc absorption and zinc status after RYGB found that zinc absorption decreased significantly, from 23.3% to 13.6%, during the first six months after surgery. Patients' zinc levels thus diminished, despite zinc supplementation at 15mg/d. However, there was a slight improvement in zinc absorption at the end of the study (18 months) [268]. In the Papamargaritis [270] study author found that zinc deficiency doubled from 7% to 15%—before and after surgery, respectively. The percentage of zinc deficiency peaked at 6 months after surgery (n=24; 13.8%). The percentage then decreased slightly throughout the follow-up period, to reach 7.1% by 36 months after surgery[270]. In contrast, Rojas, Carrasco [269] found zinc concentration levels to increase after 6 months of RYGB, despite the significant reduction in dietary intake of zinc and regardless of the supplementation group ($p<0.001$). Ruz, Carrasco [268] and Papamargaritis [270] found in cohort studies of zinc deficiency after SG, RYGB and Duodenal switch (DS), that zinc deficiency was common in 42.5% of patients, out of a sample of 324 patients at 12 months after surgery. Zinc deficiency was more prevalent in DS patients, with a percentage of 91.7% despite zinc supplementation at 22 mg/d [283]. Another cohort study compared serum zinc levels in 52 RYGB and 89 BPD patients. Zinc levels were significantly low in both groups ($p<0.0001$), however, zinc deficiency was more frequent in BPD patients—ranging from 44.9% to 74.9% deficiency Balsa [281]. Further studies have supported findings from Ruz, Carrasco [268] which showed that the peak effect of plasma zinc concentrations after RYGB occurred at ~6 months after surgery ($p<0.05$) [234, 268, 272, 273, 276, 284]. There was however some discordance on the effects of LSG on zinc levels - i.e. Pech, Meyer [236] did not find significant zinc deficiency following SG. while Katsogridaki, Tzovaras [274] found significant zinc deficiency after SG ($P<0.001$), table 2.4.

2.4.7 Effectiveness of zinc replacement to improve taste change.

Thirteen studies have examined the effectiveness of zinc replacement as a treatment for taste change. All studies are randomized controlled trials, and none was performed in BS. Five studies have examined the effectiveness of 45–50 mg of zinc sulphate supplementation either 2 or 3 times per day, in cancer patients with head and neck cancer or chemotherapy, over a treatment period ranging from 1 to 8 months [252-255, 265].

A study in 2019 study Khan [254] found that zinc sulphate was not effective in the treatment of taste alterations induced by chemioradiation (p=0.04)[254]. In contrast, in an older study conducted in 1998, authors found a significant improvement in taste—which was measured at 64% in the zinc-treated group, compared with 22% in the placebo group, after receiving 45mg of zinc 3 times per day over 1 month [255]. Both authors used detection thresholds to measure taste. Halyard, Jatoi [265] introduced 45 mg of zinc sulfate 3 times per day in a sample of 169 patients with head and neck cancer for 6 months. The investigator found no significant difference in taste improvement, in either the zinc-treated or the placebo group (p=0.09)[265]. Similarly, Lyckholm [252] did not find a significant improvement in 58 patients after introducing 50 mg of zinc sulfate for 3 months, both authors used a taste questionnaire to identify taste change. Najafizade, Hemati [253] found a slight increase in the threshold for the perception of salty taste (p=0.046). Two studies examined the effectiveness of zinc supplementation in taste disorder treatment in elderly patients, Ikeda [259] studied a large number of participants—408 patients, who received 17 mg of zinc—and found their zinc levels to increase significantly after one month of the treatment, from 69 mg/dl or lower to 91.0 mg/dl (p, 0.001). Stewart-Knox, Simpson [237] study also showed significant improvements in taste after receiving 15–30 mg of zinc over 6 months.

Six studies involved participants with taste dysfunction. All these studies reported significantly high improvements in zinc levels after zinc supplementation. They found that taste dysfunction either improved or was cured—in a treatment period ranging from 3 to 6 months with a zinc dose ranging from 20–50 mg/d [256, 262-264, 266, 267] **(Table 2.5**).

Table 2.4 Zinc deficiency following bariatric surgery. Summary of 12 studies.

Author(s), Year, and Country	Study Design and Duration	Sample Size & Age	Type of BS	Intervention and period	Weight reduction since surgery	Effectiveness of zinc supplementation	Zinc dose	% Zinc absorption
Ruz, Carrasco [268] USA	RCT; August 2004 and December 2006.	n= 67 18–55 years; F: 67	RYGBP	Group A: received the standard vitamin and mineral supplement. Group B: received the improved vitamin and mineral supplement. Before, 6, 12, and 18 months	27.9% 6 mo 35.2% 18 mo	Zinc deficiency significantly developed in both groups. By MO 6 90.9 ± 6 19.0 µg/dL; P<0.001	Standard: 7.5mg/d Improved: 15mg/d	Decreased significantly from 32.3% to 13.6% at 6 mo after RYGBP and to 21% at 18 mo after surgery.
Papamargaritis [270] UK.	Prospective cohort; 36 months	n=437patients;82 % F; Age:45.9± 11.2 years	RYGB/SG/ AGB 57%/20%/23% respectively.	Stander multivitamin supplementation; 3, 6, 12, 18, 24 and 36 months	NR	Zinc deficiency ranged from 7 to 15%. 3 MO: 18 (9.1%) 6 MO: 24 (13.8%) 12 MO: 18 (14.8%) 18 MO: 5 (12.5%) 36 MO: 1 (2.3%)	Zinc 15mg/d	NR
Balsa [281] Spain	Cohort; 5 years	n=141 patients, 52 (RYGB) and 89 (BPD).	RYGB BPD	Stander multivitamin supplementation; followed up at 3, 6, 12, 24, 36, 48 and 60 months	NR	Zinc level significantly decreased in the BPD group (P<0.0001). In RYGB zinc deficiency significantly lower at 48 and 60 months (15.4% and 21.2%, respectively)	8 mg/d	NR
Salle [283] France	Cohort; June 2005 and 2009	n=324 patients 48 M and 276 F; RYGB (n=266) or SG (n=33) or DS (n=25); Age:29–65 years	RYGB SG DS	Multivitamin supplementation; Follow up 6,12 and 24	% of weight loss 6MO: 25.2±6.6 12MO: 32.5±8.8 24MO: 33.4±11.1	% of zinc deficiency patients. 6MO: 35.6%; 12MO: 42.5%; 24MO: 34.8%; Zinc deficiency was present in 42.5% of patients at M12 and more frequent after DS (91.7%) at M12	15 mg/d	NR
Billeter, Probst [276] USA	Prospective Cohort; 2 years	20 patients 50% male Age: 18–70 years	RYGB	Multivitamin supplementation; Follow up, 3, 6, 12 and 24	NR	Zinc decreased significantly over 24 months 13.9±0.5 to 10.8±0.5. mol/l	NR	NR

Madan, Orth [284] USA	Cohort December 2002 to June 2003	n=100 patients	LRYGB	Multivitamin supplementation Follow up, 3, 6, 12	NR	Zinc deficiency 3MO 23%; 6MO 23%; 12MO 36%	NR	NR
Rojas, Carrasco [269] Chile	RCT 2004–2008	n=63 F; mean age: 36.9±9.2 years.	RYGB	Group A: received the standard vitamin and mineral supplement Group B: received the 'improved vitamin and mineral supplement'. Group C: extra zinc supplement; baseline and 6 months after RYGBP	NR	Plasma zinc concentration increased in all groups after 6 months of surgery: 8.6± 23.2 P=0.007	A: 7.5 mg/d B:15 mg/d C: 25 mg/d	NR
Gobato, Seixas Chaves [272] Brazil	Cohort	n=36 patients age: 18 to 65, 75% F	RYGB	Multivitamin supplementation; baseline and 6 months after RYGBP	The mean weight loss from baseline to 6 months after surgery was 35.34±4.82%.	(61.11%) patients reported zinc deficiency 6 months after surgery	7 mg/d of zinc oxide	NR
Pires, Martins [273] Brazil	Cohort	n=22 patients; Age 19–56 years,	RYGB	No supplementation baseline and 6 months after RYGBP	Weight after 6 months of surgery 80.50 ± 12.60 Kg	At 6 months after the RYGBP operation, the patients had decreased zinc concentration in urine compared with the initial value, and the difference was statistically significant (P<0.05).	NR	NR
Dalcanale, Oliveira [234] Brazil	Prospective cohort; 2 years	n = 75 Age: 18–65 years; M: n=7, F: n=67	GBP	Multivitamin supplementation; 2 years.	EWL% = 50% or above	40.5% of patients had zinc deficiency, which was significant (p = 0.008).	25mg/d	NR
Pech, Meyer [236] Germany	Prospective, single centre, Observational, 2005–2009	n= 82 patients underwent SG Age: 22–64 years; M: 48, F: 34	SG	33 patients underwent zinc supplementation 3, 6, 12, 18 and 24 months.	EWL% was 54.3% after 6 months and 65.3% after 12 months.	30 patients received zinc supplementation;13.4% of participants had zinc deficiency after surgery.	15 mg/d	NR
Katsogridaki, Tzovaras [274] Greece	Prospective cohort study; 2013–2015	50 patients; 14 M (28%) and 36 F (72%), age: 38.74 ±11.87 years.	LSG	6 months after surgery Multivitamin supplementation	NR	Zinc deficiency was 7% preoperative 0.70 (0.20) (p<0.001) and ranged from 7-15% post-operative 0.58 (0.19) (p<0.001) in patients receiving multivitamins and mineral supplementation post-	7 mg/d	NR

						operative, 0.11 95%CI (-0.16–0.071).		

Number =(n); Standard deviation= (SD); Male= (M); Female= (F); MO= Month; NR= Not reported; LGBP= Laparoscopic gastric bypass; LSG= Laparoscopic sleeve gastrectomy; LRYGB=Laparoscopic Roux-en-Y gastric bypass; LAGB= Laparoscopic adjustable gastric banding; RYGB=Roux-en-Y gastric bypass; SG= Sleeve Gastrectomy

Table 2.5 Zinc and taste disorder. Summary of 13 studies.

Author(s), Year, and Country	Study Design and Duration	Sample size	Age	Disease or case	Methods	Zinc dose/d	Treatment period	Outcomes
Khan [254] Pakistan	RCT Oct 2017 to Mar 2018.	17 patients 32.4% females	46 ± 9.2, 32.4% females	Chemotherapy-Related Taste alteration (oral cancer)	Detection thresholds, serum zinc level	Zinc sulfate 50 mg orally 3 times/d	7–8 MO treatment 1 MO Follow up	Zinc sulfate was not found to be preventing chemoradiation induced taste alterations. Sweet taste was most effected by cancer p= 0.04
Ripamonti [255] Italy	RCT 1995–1996	18 patients (8 F & 10 M)	Mean (SD) age 55.5 (14.39)	Head and neck cancer	Detection thresholds, serum zinc level	Zinc sulfate 45 mg orally 3 times/d	1 MO	A rapid improvement of taste was observed in 64% of patients treated with zinc, compared with 22% of the placebo group.
Sakai [256]) Japan	RCT 1991–1994	73 patients 47 F	23 to 79 years	Idiopathic taste disorder	Filter paper disk method, serum zinc level	29 mg of zinc picolinate/3 times/d	3 MO	Zinc level before treatment 69 mg/dl or lower. Patients' zinc picolinate-treated group had significantly high improvement (x2 test: p=0.01) compared to placebo
Halyard, Jatoi [265] USA	RCT 2002–2005	169 patients 118 M; 51 F (Co=84+Int=85)	≥18 Years	Head and neck cancer	Taste change questionnaire + serum zinc level	Zinc sulfate 45 mg orally 3 times/d	6 MO	No significant difference in taste between zinc-treated group and placebo p=0.09
Lyckholm [252] USA	RCT 2002–2005	58 cancer patients 41 females	≥18 Years	Chemotherapy-related taste (cancer)	Taste change questionnaire + serum zinc level	50 mg of elemental zinc/2 times/d	3 MO	There was no statistically significant improvement after zinc supplementation treatment (P<.0001
Mahajan, Prasad [266] USA	RCT	22 patients	51.3 ± 3.2	Uremic hypogeusia	Detection thresholds, serum zinc level	50 mg of elemental zinc as zinc acetate/d	6 MO	After 6 to 12 weeks of therapy, patients showed significant improvements in taste. The mean plasma zinc level increased from 75 ± 8 to 97 ± 10 ısg/dl (P < 0.001) in patients receiving zinc acetate.
Atkin-Thor, Goddard [264] USA	RCT	20 patients	21–70 years	Hypogeusia	Detection thresholds, serum zinc level, hair zinc	440 mg ZnSO4 Post-dialysis, 3 times per week	6 Weeks	After supplementation with Zn, taste acuity markedly improved in 95% of patients and Zn concentrations in hair

								increased in 85% of patients. The patients' appetites Improved
Stewart-Knox, Simpson [237] Tokyo, Japan	RCT	199 healthy older F=M	70–87 years	Taste disorder in elderly	Detection thresholds, serum zinc level	15 or 30 mg Zn/d	6 MO	Serum Zn increased post-intervention, intervention. Salt taste acuity was greater in response to Zn (30 mg) supplemented group (0·84 409 (SD 0·13 349) than the placebo group (0·75 045 (SD 0·210) post-intervention, in the Grenoble
Najafizade, Hemati [253] Iran	RCT	35 patients; (F14 & M 21)	Age=59.2±16.5, 60% male	Head and neck cancers	Detection thresholds, serum zinc level	50mg/ 3 times/d	5–9 weeks	There was a significant increase in taste perception threshold for bitter, salty, sweet and sour tastes in placebo group (p=0.001). Intervention group slight increased in threshold for perception of salty taste (p=0.046).
Sakagami [267] Japan	RCT	109 patients Placebo (n=28), Zinc-treated n=81 (56 F & 51 M)	20–80 years	Idiopathic taste disorders	Filter paper disk method, serum zinc level	17 mg (n=27), 34 mg (n_26) or 68 mg (n_28) of oral zinc, polaprezinc preparations, daily	12 weeks	Zinc level before treatment lower than 69 mg/dl The group of patients given 68 mg zinc showed a significant improvement; 25 patients cured and improved in their gustatory sensitivity, compared with the placebo group p=0.018

Ikeda [259] Japan	1 month	408 patients 228 females	49–65 years	Taste disorder in elderly	Filter paper disk method, serum zinc level	Zinc agent polaprezinc 75 mg, 2 times/day, containing 17 mg of zinc	1 MO	Zinc level before treatment 69 mg/dl or lower. 1MO after treatment had significantly increased, to 91.0 mg/dl (p, 0.001) 35 of zinc deficient patients were cured or improved of taste disorder.
Henkin, Schecter [263] Washington	RCT	106 Patients (53 M & 53 F)	19–84 years	Taste dysfunction	Detection thresholds, serum zinc level	100 mg of zinc ion in four divided oral doses	6 MO	Zinc sulfate was effective in taste treatment
Heckmann, Hujoel [262] Germany	RCT 1999 to 2001	n=50 patients (7 M & 43 F)	41–82 years	Dysgeusia	Filter paper strips and serum zinc level	140mg /d of zinc gluconate, equivalent to 20 mg/day of elemental Zinc	3 MO	Intervention group reported improvements of gustatory function after zinc treatment ($p<0.001$) taste test—before (mean SD) (17.1, 5.8) and after (9.04, 13.04); zinc in serum before (mg/dl)=(72.78,18.38) and after (81.38,19.61), and rated dysgeusia as being less severe($p<0.05$).

n=number; RCT=Randomized Controlled Trails; Standard deviation= (SD); Male= (M); Female= (F); MO= Month; Zn=Zinc; d=day; mg= milligram; ZnSO4=Zinc sulfate.

2.5 Discussion

Numerous studies have been carried out on taste change following BS. Investigators have used different methods to determine said taste change. In this review, we have found that the results differed depending on the methods used to assess taste change. For instance, survey studies found that a considerable percentage of patients claimed to have taste change following BS, at a mean time of six months post-surgery [277, 279, 280, 282], consistent with a review by Ahmed, Penney [209]. However, studies that examined taste change via experimental methods like recognition thresholds, fMRI, and the sweetness acceptability test did not find a significant change in taste following BS [275, 278]. There was however one exception, where a study found an increase in sweet taste sensitivity, 6 months after RYGB surgery [247]. It is suggested that the recognition threshold methods used in the above-mentioned studies do not reflect current changes in taste intensity, as the concentrations are more closely related to our food experiences. While the discordance between findings from self-reported compared with experimental studies may not be overtly surprising, we believe that the conclusion from self-reported studies would still play an important role in investigating the effects of BS on taste change, as this may still play an important role in patients eating behaviour. The explanation of the discordant between self-report and experimental methods maybe due to the fact that consuming certain food varieties less often after surgery might lead to heightened sensitivity, resulting in reduced ability to sense and recognise flavours. Another reason might be that frequent testing through experimental methods enhances familiarity with and enhances the capacity to recognise the taste cues throughout the evaluation. A study to validate the self-reported survey with an experimental study would be important to resolve future discordance findings between the two methods.

We suggest several reasons for taste change after BS. First, it may be associated with the rate of salivary flow after BS. Marsicano, Grec [286] found a reduction in the salivary flow rate, 3 months after surgery ($p < 0.05$). Saliva is essential to dissolve food particles and stimulate taste receptor cells on the taste buds, located on the tongue papillae. Saliva dissolves some tastants, which then diffuse to the taste receptor sites. Taste sensitivity is related to the composition of saliva, in a complex process. For example, salivary bicarbonate ions can reduce the concentration of free hydrogen ions and thereby affect the sour taste. Proline-rich proteins can affect the bitter taste. The other taste stimuli (sweet, salty, and umami) are likewise affected by different elements in saliva. Thus, reduced salivary flow affects the taste threshold following BS. Second, changing levels of Gustin concentration may also induce taste changes. As noted, Gustin is the major zinc-containing protein in the human parotid; changes therein may be linked with zinc deficiency. Shatzman, [245] found that patients with hypogeusia had low concentrations of zinc in their saliva—administering zinc to these patients was associated with increased salivary zinc content and Gustin concentrations. Third, nutritional deficiencies such as vitamin B12 deficiency may manifest as a smooth, red tongue and lead to a loss of taste perception [287].

This review also offers insight into the evidence showing that zinc deficiency was reported six months after BS [234, 268, 270, 272, 273, 276, 284]. One study showed paradoxical results, in which patients' levels of zinc concentration increased after 6 months of RYGB [269]. These results should be interpreted with caution. The authors suggest that inflammation decreases zinc levels and that reduced inflammation was observed in their subjects. RYGB patients were particularly affected by zinc deficiency, because of the restrictive and malabsorptive nature of this surgery. The exclusion of the interior part of the stomach, duodenum, and proximal jejunum after RYGB

causes a malabsorption of zinc—which is primarily absorbed in the duodenum—along with low dietary intake [288, 289]. Yet, in a comparison between different BS procedures, Salle [283] found that zinc deficiency was more frequent after DS and SG than after RYGB. Another cohort found that zinc deficiency was higher in BPD patients, compared to RYGB [281], however, Ruiz-Tovar [290] found that zinc level was in the normal range one year after SG; Zinc= 86.9µg/dl.

Despite differences in the prevalence of zinc deficiency following different BS procedures, zinc deficiency frequently occurs in all types of BS procedures. However, studies by Balsa [281] and Salle [283]. reported that the number of patients undergoing each procedure was not equal; which may influenced the reported percentage of individuals affected by zinc deficiency [281, 283]. Furthermore, most studies [273] focused on one type of BS procedure, RYGB and studied just a small number of patients [234, 268, 272, 273, 276, 284].

Studies have reported zinc deficiency, even when multivitamins and mineral supplementation were prescribed to patients following surgery. There are several possible explanations for this. First, zinc absorption decreases significantly after surgery. Ruz, Carrasco [268] found a significant decrease in zinc absorption from 32.3% to 13.6% at 6 months, after RYGB; and to 21% at 18 months after surgery (See table 2.4). To the best of our knowledge, no previous studies have specifically evaluated zinc absorption after BS, except that of Ruz, Carrasco [268]. Second, the level of zinc dosage is too low to have a significant impact on absorption. It is suggested that the standard multivitamins and mineral supplementation prescribed by surgeons in current clinical practice—at between 8–15mg of zinc—are not effective for avoiding zinc deficiency following surgery. Additional studies should be conducted, to evaluate zinc absorption after BS.

Many high-quality papers have found a significant association between taste change and zinc deficiency. While the causal link between taste and zinc deficiency after BS cannot be concluded from this review, the onset of both at approximately 6 months may suggest an indirect link between the two. Further interventional studies are required to confirm the causal link. Importantly, current evidence has shown improvements in taste function, for patients with taste dysfunction, after receiving 30–45 mg of zinc supplementation daily over six months [253, 256, 259, 262-264, 266, 267]. This is twice the dosage usually prescribed to patients following BS. This suggests that zinc is an effective treatment for taste change, in many cases of taste disorders induced by different diseases. Yet studies into taste change in cancer patients found no significant improvement after similar doses of zinc supplementation. This may be explained by several interpretations. First, a small sample size makes it difficult to detect a significant difference between the placebo and intervention groups. Second, a lack of follow-up assessment may influence the outcome. Third, the absence of a formal taste test may impact the results. Fourth, mucositis and oral infections may also influence taste changes—as may other medications taken by cancer patients—and may also be important factors in delayed zinc intervention. It is also suggested that routine zinc supplementation after BS is not effective to avoid taste change and that patients require a double dosage, based on the above-mentioned studies. We therefore believe that results from this review are in agreement with another review [291], stating that zinc supplementation may potentially be used to treat taste disorders.

A high-quality RCT of 40 subjects with obesity found that 30 mg/d of zinc supplementation for 15 weeks with a restricted calorie diet of almost 300 kcal lower than the estimated energy

requirements had a positive impact on weight reduction and appetite; the supplemented group with zinc had lower appetite and more weight reduction compared with placebo group which follow only restricted calorie diet [292].

This review also found that patients who experienced taste change had higher % EWL compared with those with no taste change. In agreement with these findings and Makaronidis, Neilson [293] found a significant correlation between taste change and per cent of weight loss following RYGB; 27.8%, n=3, compared to 23.1%, n=35 with no taste change, confounding factors including procedure and patient's selection and questionnaire design may have influenced these findings [293]. Further studies on the relationship between taste change and % EWL with a comparison between different procedures are needed. A recent study suggests that subjects with a high % EWL had a significantly decreased preference for sweet-tasting food following surgery [294]. Taste alteration also has been linked to ageing. Around the age of 60, the ability to taste gradually decreased [295]. In this review, elderly people with taste disorders showed improvements in taste sensitivity after receiving zinc supplementation [237, 259]. However, the age-related taste change after bariatric surgery has not previously been described in the current studies. This may constitute the object of future studies.

2.5.1 Strengths and limitations:

This review objectively examines the effects of zinc deficiency on taste change after BS. Several limitations need to be highlighted which may influence the interpretation derived from studies obtained from this review. One of the limitations of this study is the heterogeneity of the studies' design, including most of the cohort and RCT studies. Another limitation is the lack of studies directly examining the effect of zinc on taste change, following BS. Lastly, there are some caveats

to interpreting circulating zinc levels. All the studies measure plasma/ serum levels of zinc. While this may provide a marker of patients' circulating zinc level, it may not accurately reflect patients' zinc status, especially in non-fasting state [83]. In addition, zinc concentrations are depressed by infection and inflammation [296]. Thus, plasma zinc concentrations will potentially overestimate the extent of zinc deficiency in the setting of infection or inflammation.

2.5.2 Recommendations and implications:

1. Future studies into zinc deficiency following BS should examine zinc absorption, and compare the degree of absorption in different types of BS.
2. More RCTs are needed to examine the effectiveness of zinc in taste change treatment following bariatric surgery, to obtain more reliable results.
3. Studies to link taste change with zinc levels to weight loss or weight regain.
4. More RCTs are required to examine the association between taste change and saliva flow rate, leading to more reliable results.
5. The time, dosage, and duration of supplementation need further investigation. RCTs into the effectiveness of zinc in taste change treatment used zinc supplementation of around 45–50 mg, 2 or 3 times per day, and found it effective in taste change recovery. However, in current clinical practice, patients still receive only between 8–15mg of zinc supplementation.

2.6 CONCLUSION

In conclusion, although a causal link cannot be established, zinc deficiency appears to be linked with taste change following bariatric surgery. Supplementation with much higher doses of zinc—45-50 mg—has been effective in taste change treatment for 3-6 months, for many cases of taste disorder. The results of this systematic review are in agreement with the updated BOMSS

guidelines that BS patients need high doses of zinc supplements and that zinc deficiency occurs most frequently after the Duodenal switch (DS). Yet routine multivitamin and mineral supplementation prescribed to patients following BS, in current clinical practice, is currently ineffective at avoiding zinc deficiency following BS. It is therefore also ineffective at avoiding taste change. Taste change is more frequent after the RYGB procedure compared to other types of BS procedures, More research is crucial, to explore the association between zinc deficiency and taste change following BS—as well as the effect of BS in zinc absorption—and to ensure that BS patients are being given the level of zinc supplementation they require. Evidence derived from this systematic review has identified some research gaps in this research area which informs the objective and design of the following chapter in this thesis to investigate the incidence and prevalence of taste change (using mixed methods) following two types of bariatric surgery and to link it with changes in zinc level.

Chapter 3: Materials and Methods

Chapter overview

Study 1 and 2 in the first section of this thesis was informed by the findings of the systematic review in Chapter Two.

3.1 METHODS

3.1.1 Study 1 and Study 2

3.1.1.1 Design

The first section of this thesis included two single-centre prospective observational studies based at King Abdullah Medical City conducted between March 2021 to September 2022, Makkah, Saudi Arabia, under the School of Medicine, University of Nottingham, United Kingdom. As this was an observational evaluation study, we did not perform formal power calculation.

Study 1: Associations between zinc deficiencies, taste changes and salivary flow rates following bariatric surgery (Chapter 4a)

Research question: Is there a link between taste change and zinc following BS?

Study 2: Serum zinc levels as a predictor value of hair loss following sleeve gastrectomy and gastric bypass (Chapter 4b)

Research question: Is there a link between hair loss and zinc following BS?

3.1.1.2 Main aim

To study the potential links between circulating zinc levels, taste change and hair loss following BS.

Objectives

To examine the prevalence of taste change following sleeve gastrectomy and gastric bypass.

To investigate the difference in circulating zinc levels following sleeve gastrectomy and gastric bypass.

To measure the salivary flow rate following sleeve gastrectomy and gastric bypass.

To examine the prevalence of hair loss following sleeve gastrectomy and gastric bypass.

To investigate the prevalence of zinc deficiency in people reporting hair loss after sleeve gastrectomy and gastric bypass.

3.1.1.4 Ethical consideration

Ethical approval was granted by the institutional review board at King Abdulla Medical City, Ministry of Health, Kingdom of Saudi Arabia (IRB number 20-719) on the 14th of February 2021. Subsequently, ethical approval was extended for one year and the ethical approval letter was received on the 31st of March 2022.

3.1.1.5 Duration of the study and participant involvement

Following receipt of ethical approval, recruitment commenced in February 2021, and the study continued until September 2022. Each patient participated in the study for six months. The study began when the patients attended the first study day (when the first blood sample was collected) and was concluded on the patient's final procedural day.

End of the study

The end of the study was the last procedure (study) day of the final participant.

3.1.1.6 Bariatric surgery procedure:

The surgeons in KAMC used the following methods for Gastric bypass (GB), and sleeve gastrectomy (SG). These steps are developed from the following sources [297-300].

Sleeve Gastrectomy:

The initial step involves the positioning of the patient and the installation of ports. Following this, the patient is positioned in the supine position and subsequently adjusted to the Trendelenberg position. A port with a diameter of either 12mm or 15mm is positioned at the umbilicus (or at a superior and rightward location, contingent upon the patient's size and the presence of a pannus). A Nathanson liver retractor (a 3mm or 5mm subxiphoid variant) is utilised to retract the left lateral section of the liver.

The surgeon may employ a 5mm, right upper paramedian port to facilitate movement of their left hand, while the assistant may utilise a 5mm left anterior axillary line port to support the actions of their right hand. A 5mm port is positioned in the left upper paramedian region to accommodate the scope. The second step involves the process of stomach mobilisation (mobilisation of the fundus). Utilising the designated energy source, the surgeon will create an aperture within the omental bursa, situated at a distance of 4 to 6 centimetres from the pyloric region. In a superior manner, the short gastric veins are to be sealed and divided immediately on the serosa of the stomach. Cease forward movement and initiate a reversal of course upon encountering challenges in the process of exposure. The mobilisation of the antrum: When nearing the pylorus, it is important to take note of the transformation of the gastro-duodenal artery and the right gastric artery into the gastroepiploic artery. Typically, the cessation of the dissection around 2 centimetres

proximal to the pylorus is an effective measure to avoid potential harm to the veins in question and to ensure an adequate blood supply to the distal antrum and pylorus.

Activation of the cardia: following mobilisation of the antrum, the retraction of the stomach towards the patient's right and inferiorly will provide improved exposure of the cardia, spleen, and left crus. The ultimate posterior short gastric can be partitioned along the left crus. The enlargement of the anterior fat pad frequently hinders the vision of the medial cardia and distal oesophagus. The objective is to mobilise this region to ensure sufficient visibility for the proper positioning of staples and sutures. The third step of the procedure is gastrectomy, specifically focusing on the antrum. A 32 French orogastric bougie is positioned close to the pylorus. The use of the 32 French bougie is based on its ability to prevent stenosis while simultaneously reducing the likelihood of antral and pouch dilatation, making it the optimal choice in terms of size. A 60 mm cartridge, either black or green, is utilised for stapling purposes around 2 to 3cm proximal to the pylorus. Seromuscular fracture is a frequently observed occurrence in this particular location while utilising any variant of a staple cartridge, necessitating the implementation of sutures for reinforcement.

The angularis/fundus is a region of the stomach. The second cartridge is located near the angular, and it is important to use caution to prevent stenosis in this area. The optimisation of cartridge placement involves the assessment of both anterior and posterior positions of the anvil and cartridge. In this particular locality, cartridges of the colours black, green, or purple are permissible for usage. It is not recommended to utilise smaller stapler cartridges. The potential benefits of greater haemostasis must be weighed against the risk of staple line disruption in the future. Buttress material can be employed to achieve haemostasis; nevertheless, it is advisable to refrain from

under-sizing the cartridge when utilising thicker materials. The term *cardia* refers to a specific anatomical structure within the human body. The positioning of the final two cartridges in the upper region of the stomach may be the greatest challenge in achieving accurate calibration. Rotating the stomach and the stapler anteriorly is a crucial step in the examination and retraction of the posterior gastric wall through the cartridge before its closure.

Gastric bypass

The treatment commences by creating a pneumoperitoneum via the left subcostal space. The initial trocar, approximately 10 mm in diameter, is inserted at the midpoint of the line between the xiphoid process and the umbilicus. This trocar serves as the entry site for the camera. The placement of second trocar, measuring 12 mm in diameter, is situated 5 cm to the right of the first trocar while maintaining the same vertical alignment. Subsequently, the third trocar, measuring 12 mm in diameter, is introduced at a distance of 5 cm to the left of the initial trocar, maintaining the same vertical alignment. The fourth trocar, whose purpose is to facilitate the entrance of the liver retractor, has a diameter of 5 mm and is placed into the right flank, specifically at the lower edge of the liver in the internal view control. The placement of the fifth trocar (5 mm) occurs in a left sub-costal location, maintaining a distance of 10 cm from the second trocar.

After the necessary preparations have been made in the operation, the esophagogastric junction is subsequently located. The initial stage involves creating an aperture in the gastric fundus located at the esophagogastric junction. This enables the retrieval of the posterior wall of the stomach and facilitates the subsequent formation of the gastric pouch.

Next, the surgeon proceeds to the lower curvature and pinpoints a certain location situated at the level sometimes referred to as the ‘crow's foot.’ Close to the gastric serosa, a perforation is initiated

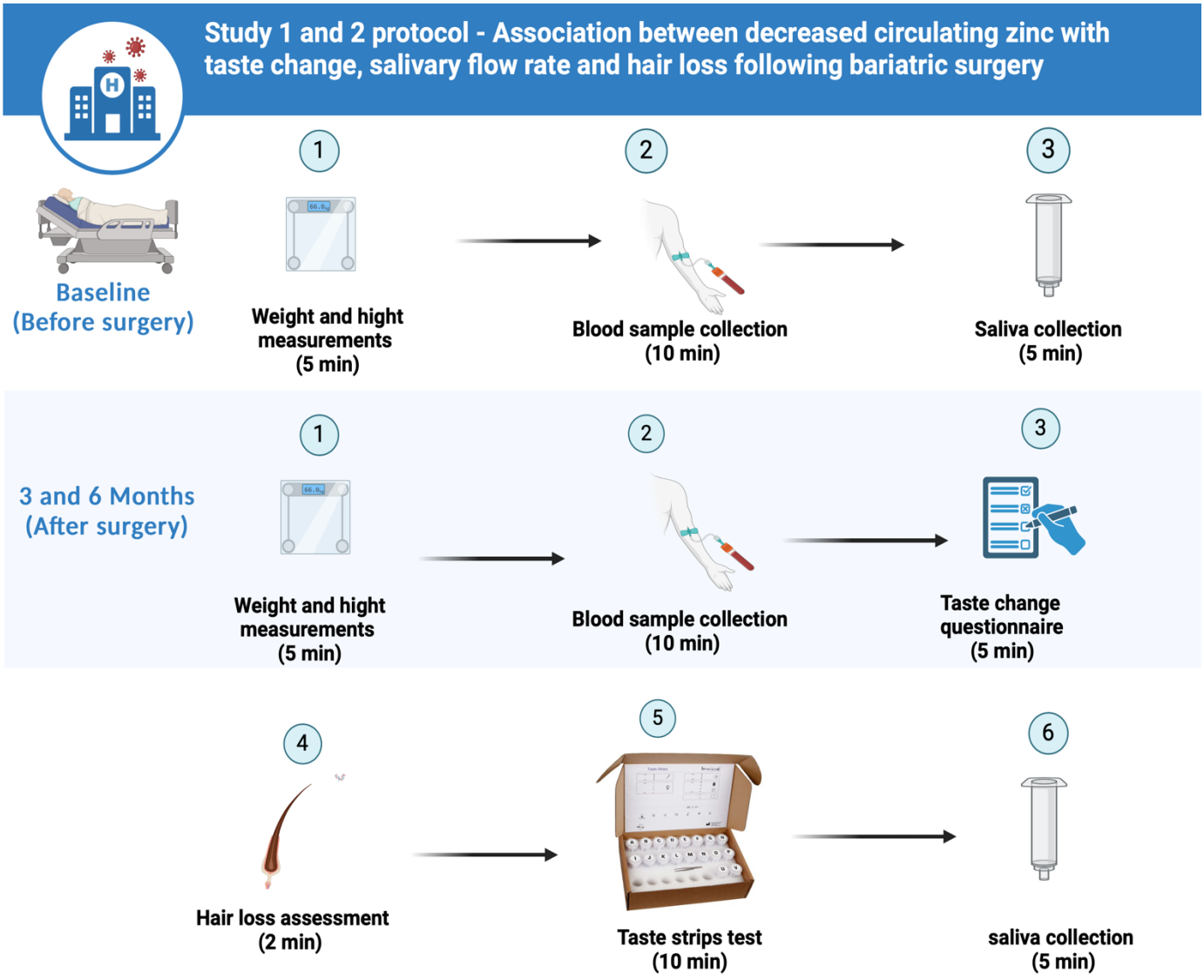
to facilitate entry into the posterior wall of the stomach. Upon reaching the posterior wall of the stomach, insert a 45 mm Endo GIA device (manufactured by Tyco®) equipped with a 3.5 mm cartridge to perform a horizontal transection of the stomach. The next stage concerns a vertical transection of the stomach, continuing until the surgeon reaches the junction of the oesophagus and the stomach. To assist in this process, a 1 cm nasogastric tube is positioned along the lesser curvature of the stomach as a guiding tool. To perform gastric transactions, employ two or three 60 mm Endo GIA (3.5 mm cartridges). In some cases, there may be a requirement for an additional Endo GIA cartridge with dimensions of either 30 or 45 mm.

Following the creation of the gastric pouch, a sixth trocar (5 mm) is inserted at McBurney's site. The surgeon is then required to identify the angle of Treitz and measure approximately 2 metres of the jejunum distally from this specific location. Following identification of the specific location, a rubber band of 10 cm in length and 0.5 cm in width is placed around the small intestine. The jejunal loop is approximated to the gastric pouch using a grasp.

In the context where both the jejunum and the staple line of the gastric pouch are aligned next to one other, the fixation process involves using 6 to 10 sutures with the assistance of an Endo stitch (Tyco®). Once both components have been stabilised, the surgeon will perform an anastomosis between the stomach pouch and the cartridge (Tyco®) is utilised to introduce a specific portion of an anastomosis, with the length ranging from 15 to 20 mm. The gastric and jejunal apertures are effectively sealed by employing a range of 4 to 6 sutures. To assess the integrity of the anastomosis, a saline solution is applied and a volume of 60 to 100 ml of air is introduced via the nasogastric tube. The absence of any observable air bubbles emanating from the anastomosis indicates a secure

closure. The anastomosis is secured via the use of 2 ml of Tissucol® fibrin glue. A suture is applied between the intestinal loop and the stomach antrum to alleviate stress on the anastomosis and prevent tension. The utilisation of omentum to provide coverage for gastro-jejunal anastomosis is a consistent practice in the performance of an omentoplasty.

Figure 3.1 Study 1 and 2 Protocol.



Created with BioRender.com

3.1.1.7 Study Procedure

This study involved the following methods to achieve the study objectives:

Measurement of the weight and height

For measuring height, the participant was instructed to take off shoes and heavy clothes, then stand with their back facing the height regulation. Ensure that the occiput, scapulae, sacrum, and heels are aligned with the stadiometer. Ensure that the body posture does not affect the vertical position of the stadiometer. The subject was instructed to stand in a natural upright stance with weight equally distributed on both feet and arms swinging freely by their side. The individual should stand at their maximum height and gaze straight forward, then record the height measurements. For measuring weight, position the scale on a firm floor surface. Participants were instructed to remove their shoes and heavier clothing items such as jackets and belts. They were instructed to stand in the middle of the platform with arms swinging freely, weight equally distributed on both feet, looking straight ahead, and feet aligned with the hips. The recorded weight is then documented [301].

Serum zinc level

The zinc level was measured at baseline, three months, and six months, following surgery.

Sample requirements

A nurse at the nutrition and obesity surgery clinic obtained blood samples from the participants at baseline, three months, and six months following surgery. The blood samples (2 - 3 ml) were placed into a trace element tube then the blood serum was extracted, placed in a serum blood sample tube, and transported to a private laboratory for same-day analysis. Zinc analysis test is performed by atomic absorption spectroscopy, Normal range for zinc is 70-120 mcg/dl



Figure 3.2 Blood sample tube - dark blue top

.



Figure 3.3 Serum blood sample tube.

Taste Change Assessment

A. An assessment of taste change was conducted at three months and six months following surgery via the use of a taste change questionnaire - See Appendix 4 (Zerrweck et al., 2015).

B. Taste Strips Test:

Taste strips are strips of filter paper infused with solutions representing four fundamental taste qualities (sweet, sour, salty, and bitter) at varying concentrations. The concentrations of the taste solutions are as follows:

- Sweet: sucrose concentrations of 0.4, 0.2, 0.1, and 0.05 g/ml.

- Sour: citric acid concentrations of 0.3, 0.165, 0.09, and 0.05 g/ml.

- Salty: sodium chloride concentrations of 0.25, 0.1, 0.04, and 0.016 g/ml.

- Bitter: quinine-hydrochloride concentrations of 0.006, 0.0024, 0.0009, and 0.0004 g/ml. These taste strips have been validated for use in both adults and children; the methodology is widely embraced, particularly among the younger demographic of children and adolescents, and has been employed in several therapeutic and research settings.

The outcomes of this examination provide an assessment of the ability to discern four fundamental flavours. The test-retest reliability of this study exhibits favourable comparability with other taste tests. During the experimental procedure, a strip is positioned on the anterior midpoint of the tongue and the participant is required to indicate the experienced flavour from a series of choices (salty, sour, sweet, bitter, or absence of taste) on a response chart. To acquaint participants with the experimental protocol and assess their ability to accurately discern various tastes, strips containing the most concentrated form of each flavour (referred to as "taste high") were randomly provided at the start of the experimental paradigm. The participants were instructed to utilise the response chart to identify the taste and subsequently received feedback following each presentation. A total of sixteen strips, each impregnated with a distinct flavour, were utilised in this study. These strips were divided equally into four concentrations, with four strips representing each concentration. Additionally, three blank strips, which were not impregnated with any taste, were included. The presentation of these strips to the participants followed a pseudo-randomized order, with an inter-trial period of twenty-five seconds.

Description:

Taste strips are a validated examination paradigm created to examine taste ability. They

are used by placing them on a patient's tongue and closing the mouth (the patient may move their tongue throughout the process). If there is interest in the gustatory sensitivity of a certain area of the tongue, the mouth remains open, and the strip must remain in its current position until the patient can provide an answer.



Figure 3.4 ODOFIN taste strips.

ODOFIN taste strips are a proven method for assessing taste sensitivity. The kit is comprehensive in nature and has the capacity to assess the gustatory acuity of a total of 50 individuals. Taste strips are administered by placing them on the tongue and closing the mouth (with the possibility of the patient moving their tongue). If there is a desire to investigate the gustatory sensitivity of specific regions of the tongue, such as by lateralized testing, the mouth is maintained in an open position and the strip remains in contact with the targeted location until the patient is able to provide a response.

The set has 16 containers, each containing 4 distinct strengths of sweet, sour, salty, and bitter flavours, and an additional 3 containers containing blank strips. The collection comprises 19 containers, each containing 50 strips, resulting in an overall total of 950 strips.

Test condition and preparations:

Before the test, the participants are asked to only consume water and are requested to adhere to several restrictions including to refrain from smoking, eating, and chewing gum. The test supervisor should arrange the test materials on a table and ensure that the participants have access to water that is low in salt, low in minerals, and uncarbonated. Additionally, a waste container

should be positioned in front of each patient for their convenience. Finally, the supervisor should prepare the test materials by opening the package and placing the containers holding the strips carefully on the table.

Presentation of strips

To begin the procedure, it is recommended that the tweezers be held in one hand while the other hand is used to open the container. Tweezers should be used to extract the taste strips; if the strips in the container come into contact with bare skin, the container should be considered contaminated and disposed of appropriately. The strip is designed for single-patient usage.

Test sequence

The nineteen flavour strips are sequentially presented in a pseudo-randomized fashion. Once a participant has identified the taste of the strip, it should be disposed of, and it is recommended that they rinse their mouth with the water provided. In addition to the strips that have been impregnated, it is possible to provide strips that are devoid of any flavour (referred to as Blanks U+V). As a suggestion, it is advisable to provide a single strip at the commencement of the examination to exemplify the flavour of the paper.

Whole mouth testing

Each patient was provided with an initial taste strip and provided with the following instructions: to get the chemical to dissolve in the saliva, place the strip in the centre of the tongue, close the mouth, and move the strip slowly back and forth. Patients were also provided with the option of flipping the strip over and repositioning it on the tongue. It is necessary to rinse the mouth with water after each tasting.

Patient's evaluation

The patient is required to identify the taste of each strip. They were provided with the following options: sweet, sour, salty, bitter, and no taste. The summary paper will include the responses.

Evaluation

Each flavour quality has four correct identifications, and each correctly identified taste strip is awarded one point; therefore, if all sixteen strips are properly recognised, the highest achievable score is sixteen. The presence of blank (flavourless) test strips is not accounted for or considered throughout the evaluation process, although incorrectly identified strips retain the potential to form part of the diagnostic process for individuals exhibiting the symptoms of parageusia. Individuals suffering from acute hypogeusia occasionally experience difficulty in discerning strip properties, even when the concentrations are increased. As a result, individuals who have impaired perception and inaccurate recognition of the most intense levels of sensory stimuli (A, E, I, M) do not experience a complete loss of taste for the corresponding attribute. Patients exhibiting hypogeusia, characterised by a flavour identification score of less than 9, may have ageusia, or the complete loss of taste perception, for certain taste attributes. The normative values for each taste quality are displayed in the following table.

Table 3.1 Taste strips evaluation criteria.

	Number of correctly identified taste qualities				
	Sweet	**Sour**	**Salty**	**Bitter**	**Total score**
Normogeusia	>=2	>=2	>=2	>=1	>=9
Hypogeusia	1 or false identification	1 or false identification	1 or false identification	False identification	<9
Ageusia	No sensation	No sensation	No sensation	No sensation	No sensation (Complete ageusia)

When an individual's taste perception rating falls below the threshold value of 9, hypogeusia can be diagnosed (regardless of age). A patient who is unable to identify any of the flavours (A-sweet, E-sour, I-salty, and M-bitter) at maximum concentration levels can be comprehensively diagnosed with ageusia. When analysing the test results, it is possible to assess the overall taste performance as well as the individual performance for each flavour quality. As an illustration, individuals experiencing hypogeusia, with a total score of 7, may exhibit partial ageusia specifically for sour tastes, characterised by the absence of perception in the sour taste sensation.

Labelling the containers and strips

The container's cap and strips are labelled with the letters A to P and U+V as illustrated in the following table.

Table 3.2 Labelling the containers and strips.

Highest concentration	A	E	I	M	U+V
	B	F	J	N	
	C	G	K	O	
	D	H	L	P	
Lowest concentration	**Sweet**	**Sour**	**Salty**	**Bitter**	**Blanks-no taste**

Additionally, the containers are marked with an expiration date, using the format dd-mm-yyyy, and stored in a clean, dry environment at room temperature (between 10°C and 20°C)

Appetite Assessment

The Council on Nutrition Appetite Questionnaire (CNAQ) was used to assess the appetite of the participants, However, the appetite results are not reported in the thesis (See Appendix 4).

Salivary flow assessment

Salivary flow rates were assessed in the stimulated and unstimulated conditions using the methodology suggested by Navazesh [302]. Salivary flow rate assessment measures saliva production in subjects required to chew on a section of tasteless Parafilm® which is the preferred technique due to its simplicity and effectiveness at acquiring an appropriate amount of saliva. The production of saliva is mostly attributed to the parotid gland, which is activated by several stimuli such as mastication, taste, and oesophagal stimulation. The process of evaluating stimulated flow entails the collection of a saliva sample for five minutes. In this study, stimulated saliva was collected by asking individuals to chew continuously on a clean square of Parafilm® for five minutes. Every time the individual felt the urge to swallow (which was not permitted in this test), they were asked to expectorate their saliva into a sterile, graduated polypropylene collection tube. Following collection, any salivary foam was allowed to settle, the volume (mL) was recorded, and the stimulated salivary flow rate (SFR) was determined (ml/min).

The salivary flow was classified based on the quantity of saliva collected: Very Low (< 3.5 ml); Low (3.5 - 5.0 ml); and Normal (> 5.0 ml). The collection process was conducted at baseline, after three months, and after six months following surgery.

Hair loss Assessment

Patients were questioned regarding hair loss and were required to select using one of the following options: severe hair loss, moderate to mild hair loss, or no hair loss. An alternative test that could be use is the hair pull test, This is a straightforward bedside test used to evaluate the existence of ongoing hair loss. To do the action, one should firmly hold a cluster of around 50 to 60 hairs between the thumb, index, and middle finger, and then gently tug on the hair shaft from the scalp towards the ends of the hair. A positive pull test and active hair loss can be determined by the presence of more than 5 to 6 hairs that can be easily extracted. It is necessary to do this test throughout all areas of the scalp. Patients must refrain from washing their head for a minimum of 24 hours before to the test [303].

Selection and Withdrawal of Study Participants

The primary factor considered for selecting the participants of this study is that they must have been registered for GB or sleeve gastrectomy bariatric surgery in KAMC (confirmed via registry records and a review of medical records).

3.1.1.8 Inclusion Criteria

All interested subjects who meet the following criteria:

1. Obese (BMI≥35), adult (≥18 years) patients scheduled for GB or SG at King Abdullah Medical City, Makkah, Saudi Arabia.
2. Capability to give informed consent.

3.1.1.9 Exclusion Criteria

Subjects will be excluded if patients:

- Are scheduled for other forms of bariatric surgery (banding, duodenal switch, biliopancreatic diversion, gastric balloon and gastroplasty).

- Have a zinc deficiency before surgery.
- Receive medication that could alter taste function.

3.2 DATA COLLECTION

3.2.1 Recruitment of subjects

Subjects were recruited from the obesity clinic (Tier 4) at King Abdullah Medical City (Makkah). They were scheduled for GB and met all of the pre-existing criteria for GB and SG, including a body mass index (BMI; calculated as kg/m^2) greater than or equal 35 kg/m^2 and an inability to achieve weight reduction after multiple dietary treatments. Participants was informed that entry into this study is entirely voluntary, and they may withdraw their participation at any time. If patient have COVID-19 he/she was asked to attend the visit two weeks after the infection. All participants were asked to take multivitamins supplementation centrum supplementation for at least 6 months following sleeve gastrectomy operations, and for life after GB surgeries. The single tablet serving for this supplement contains only 5 mg of zinc.

3.1.1.10 Informed Consent

All participants were required to provide informed written consent which must be signed and dated before starting the study. The researcher will explain the study details to participants and provide them with a participant information sheet. All subjects underwent a medical examination involving an analysis of their medical history, a physical examination, measurement of their height (cm) and weight (kg), calculation of their BMI, and blood tests.

3.1.1.11 Sample Size and Justification

This study targets a participant population of thirty patients. This is an exploratory evaluation study: no previous study has been performed.

3.1.1.12 Study Visits

First visit (before surgery)

A blood sample was collected, and the height, weight, BMI, and salivary flow of each participant were determined.

Second visit: After 3 months

In the second visit, the patient's height, weight, BMI, hair loss and salivary flow was measured, and a blood sample was taken. Additionally, the appetite assessment questionnaire and taste change questionnaire and test were conducted.

Third visit: After 6 months

On the third visit, the researchers conducted the same processes as the second visit.

3.1.1.13 Statistical Analysis

Basic descriptive statistics summarized patients' demographics, body weight (kg), height (cm), BMI (kg/m^2) and zinc levels (mcg/dl) at baseline. Person Chi-square was used for the difference in proportions, P-value of 0.05, also used to test differences in proportions between bariatric groups on hair loss at 3-and 6- months of follow up. While † Fisher's exact test for low expected frequencies was used for the taste change questionnaire outcome (i.e. 20% of the expected frequencies at < 5), P-value of 0.05. † Fisher's exact test was also used for the outcomes of the taste strips test to illustrate the % of overall hypogeusia and % of hypogeusia in each taste quality during the follow-up period, among patients who underwent sleeve gastrectomy and gastric bypass. Student's t-test statistics were performed to obtain possible meaningful differences in means between bariatric groups regarding their zinc levels as well as their body weight reductions,

compared to their baseline status, throughout the follow-up time. The paired t-test uses the existing data as it drops participants with no record at 6 months point to activate the 'Before & After' analysis. While the test for a difference was performed using unpaired t-test for parametric variables.

Ethical Considerations and Confidentiality:

To participate in this study, all of the participants were required to sign the informed consent form. Ethical approval was be sought from KAMC, IRB and no study activities were commenced before receiving this approval.

Chapter 4a: Associations between decreased circulating zinc levels, Taste Changes and Salivary Flow Rates Following Bariatric Surgery.

Chapter Overview

This chapter includes the study 1, which aims to investigate the association between taste change and decreased circulating zinc following BS. In addition to examining the salivary flow rate following BS. This chapter also compare the outcomes difference between Gastric bypass (GB) and sleeve gastrectomy (SG) procedures. The findings indicated that, the observed changes in zinc levels subsequent to GB were found to be parallel to the overall changes in taste, in contrast to the alterations observed following SG. Most patients who had undergone bariatric surgery (BS) experienced decreased salivary flow rates, ranging from low to extremely low, throughout the postoperative period. The findings of this chapter have been published in *Journal of Nutrition and Metabolism in March 2024*

4a.1 ABSTRACT

Background: The prevalence of hypogeusia after bariatric surgery and the link between hypogeusia and circulating zinc levels is unclear, with different methods of assessment of hypogeusia may affect the outcomes. We therefore, aim to investigate the prevalence of hypogeusia using the questionnaire and taste strip methods along with changes in salivary flow rate and to assess the link with changes in zinc level following gastric bypass (GB) and sleeve gastrectomy (SG).

Setting: Single center study (KAMC) Hospital.

Methods: This was a prospective observational study of GB (N=18) and SG (N=25). Hypogeusia was evaluated using a validated questionnaire and by taste strips procedure along with serum zinc levels and salivary flow rate.

Results: Mean age was 40.0±9.7 years; 60.5% were female. Using the questionnaire, GB patients experienced greater hypogeusia than SG at 3 months 72.0% vs 36.0% (p=0.03), but not at 6 months 56.0% vs 45.0% (p=0.74) respectively. Using taste strips, at 6 months, a greater percentage of GB patients experienced hypogeusia compared with SG (44.0% vs 11.0%, p=0.052). Zinc levels were reduced following GB at 6 months compared to baseline 85.6±16.9ugm/dl vs 67.5±9.2µgm/dl, but were increased at 6 months following SG (76.9±11.4 vs. 84.9±21.7µgm/dl). There was a significant difference in zinc levels between GB and SG at 6 months P= 0.004. Reduction in the rate of salivary flow was observed in 66.0% and 72.0% of GB and SG patients respectively at 3 months and in 47% and 70.0% at 6 months.

Conclusion: Taste change is more prevalent following GB compared with SG using survey and taste strips, especially at 6 months after surgery which parallel with changes in zinc levels. More than half of all patients who had undergone BS had low to very low salivary flow rates during the

follow-up. This study suggests a potential association between decreased circulating zinc levels and reduced salivary flow with hypogeusia following BS.

4a.2 Highlights

• Both gastric bypass (GB) and Sleeve Gastrectomy (SG) were potential associated with increased rates of hypogeusia post-surgery, but the GB procedure led to significantly higher rates of hypogeusia compared with SG at 3 months (72.0% vs 36.0%; p=0.03 using questionnaire), and at 6 months (44.0% vs 11.0%, p=0.052 using taste strip)

• There were minor differences in the outcomes between questionnaire and taste strip assessments of hypogeusia but both methods concluded a higher rate of hypogeusia with GB compared with SG.

• Lower zinc levels were observed at 6 months after gastric bypass compared to sleeve gastrectomy.

• Both procedures lead to a reduction in salivary flow rate in more than 50% of patients, which may also contribute to the prevalence of hypogeusia with both surgical procedures.

• Our study may suggest a potential link between lower zinc levels, hypogeusia and reduced salivary flow following bariatric surgery, especially after gastric bypass.

4a.3 Background

Studies have reported abnormalities in taste (hypogeusia) as a typical adverse effect of BS. According to one report, 73% of patients who had RYGB experienced hypogeusia [280], while another study reported hypogeusia in 64% and 59% of patients post RYGB and SG respectively. These studies also showed that hypogeusia is associated with a higher % weight loss following RYGB; however, not post-SG [293]. Prevalence data for hypogeusia however is affected by differences in the methodologies used with respect to indirect vs. direct measurements. For example, a review in 2019 found that, in most studies utilising surveys and questionnaires, individuals self-reported changes in taste and a decline in cravings for energy-dense foods such as sweets and high-fat foods. Conversely, research employing proven sensory approaches, such as oral sampling or direct food intake measures indicates little to no change in the ability to perceive taste or in evidenced preference for consuming energy-dense meals [304]. A subsequent review in 2022 also found that studies using surveys reported a considerable percentage of patients reporting experiencing taste changes following BS, while studies that assessed taste alteration using experimental approaches such as recognition thresholds, fMRI, and the sweetness acceptability test did not identify any significant effect of changes in taste after BS administration [305].

Taste change can also be an indicator of hypofunction of the salivary glands, which results in decreased salivary flow (SF) rates. Saliva is crucial to the taste response, as it speeds up the transduction of tastants by solubilising and accelerating their passage to the taste pore where they attach to receptor cells [170]. It also has lubricating and antimicrobial effects, as well as containing the growth hormones that help taste receptors regenerate [306], all of which can be affected by BS [307].

The precise underlying mechanism for taste alteration following BS remains unknown. There is evidence that BS significantly causes an increased risk of micronutrient deficiency. Zinc in particular is an important element for taste bud development in healthy individuals and plays an important role in saliva secretion [240, 308]. Since patients who underwent malabsorptive procedures are at a higher risk for developing zinc deficiency, the British Obesity and Metabolic Surgery Society (BOMSS, 2020) recommends targeting a ratio of 8 to 15 mg zinc to 2 mg copper in supplementation. The acceptable upper consumption limit for zinc is 40 mg per day for those aged 19 years of age and older [6], aiming for serum or plasma zinc level of between 80 to 120 mcg/dL (12 to 18 mcmol/L).

Previous studies examining the prevalence of hypogeusia have used different methodologies and did not undertake concurrent assessment of zinc levels for different BS procedures. This study therefore aimed to assess the prevalence of GB and SG using a mixed method approach, applying both questionnaires and taste strips to determine the link, if any, between zinc and post-operative taste and salivary flow rate changes.

4a.4 Methods:

As described in Chapter 3.

4a.5 Results:

4a.5.1 Patient demographics

56 participants were included at baseline; however, 13 individuals withdrew. Reasons for withdrawal were a large distance from the study site and therefore not being able to attend follow-up visits (N=5), no reason provided (N=8); 43 adult patients who had undergone BS at the KAMC facility were included in this study. Patients who underwent GB (N=18) were compared with patients who underwent sleeve SG (N=25). The basic data for both groups was as follows: female 60.47%, male 39.53%; mean age: 40.03 (SD: 9.7) years; total follow-up period was 6 months; mean body weight, BMI and zinc levels at baseline were 117.3 (SD: 27.4) kg, 42.7 (SD: 8.29) kg/m^2, and 81.4 (SD: 15.0) mcg/dl; respectively. All patients received multivitamins supplementations containing 5mg of zinc. All GB patients underwent SG for at least 4 years before GB surgery. More specific patient characteristics for each group are presented in *table 4.1.*

Table 4a.1 Patient characteristics at baseline.

	Sleeve gastrectomy (N=25)	**Gastric bypass (N=18)**
Age, mean (SD)	38.12 ±11.58	41.88±7.41
BMI, mean (SD)	45.90 ±6.63	39.46 ±8.68
Body weight kg, mean (SD)	125.9 ±23.57	108.95±28.60
Zinc mg/dl, mean (SD)	76.90±11.41	85.6 ±16.9

4a.5.2 Zinc levels and prevalence of hypogeusia

There was a numerical decrease in zinc levels after SG at the 3-month follow-up when compared to baseline (73.8±15.7 vs 76.90±11.41). Similarly, there was a numerical decrease in zinc levels after GB at the 3-month follow-up when compared to baseline (70.7± 14.43 vs 85.64 ±17.0). At

the 6-month point, zinc levels increased among SG patients (84.9±21.6) while decreasing further among GB patients (67.5±9.16). Thus overall, zinc level increased significantly (by 13.4 mg/dl) for patients who underwent SG between 3 and 6 months of follow-up ($t(19) = -2.40$; $p = 0.027$). Whereas for GB patients, zinc level remained at similar levels during the same period of follow-up (1.44 mg/dl difference, $p = 0.59$. These changes in zinc levels corresponds with the percentage rates of hypogeusia in each case, indicating a negative relationship between zinc levels and hypogeusia. At 6 months following SG, the mean zinc level increased reaching 84.9±21.6 mg/dl; compared to the 3 months, and this seems to be associated with a decrease in the hypogeusia percentage; 11.0% at 6 months vs 36.0% at 3 months. Zinc levels among GB patients, however, were decreased at the 6 months of follow-up as compared to that at 3 months, and this corresponds to the increased numbers of patients experiencing hypogeusia 44.0%.

The results from the taste strips test showed that GB patients experienced high rates of overall hypogeusia at 6 months post-surgery (44.0%). Zinc levels were also lower on average at 6 months post-surgery, at 67.5±9.16 mg/dl, as compared to those at 3 months at 70.7 ±14.43. Sweet and salt hypogeusia occurred most frequently, and the sense of taste that did not change between the four basic taste qualities was that corresponding to bitterness. However, SG patients experienced a high rate of overall hypogeusia at 3 months (36.0%) and decreased at 6 months (11.0%). The mean zinc levels were low at 3 months, at 73.8 ±15.7 mg/dl and improved at 6 months to 84.9±21.6 mg/dl. Most participants demonstrated sweet hypogeusia, with varying rates of sour, salt and bitter hypogeusia. Hypogeusia among SG patients was found to be more frequent at 3 months and decreased at 6 months post-surgery. The sense of taste that was less affected by hypogeusia between the four basic taste qualities was again that corresponding to bitterness.

In total, 25 patients completed the 3-month follow-up and 20 completed the 6-month follow-up survey post-SG surgery, while 18 patients completed the 3-month follow-up and 17 completed the 6-month survey post GB surgery. The results of assessing both sets of data indicated that patients across both surgery procedures experienced a considerable rate of hypogeusia during the study period. However, the GB patients were more significantly affected than the SG patients. 36% of SG patients experienced hypogeusia at 3 months, with this percentage increasing further by 6 months to 45%. In contrast, almost three-quarters (72%) of GB patients experienced hypogeusia of taste change percentage at 3 months and 56% at 6 months. A much smaller number of patients among both groups reported complete loss of taste, and again the percentage among GB patients was higher than among SG patients. The figures for this were 8% and 10% at 3 and 6 months respectively for SG patients versus 33% and 31% at 3 and 6 months, after GB. With respect to taste categories, the most notable change in taste was seen for sweet tastes, which was significant as compared to changes for the other categories (sour and salt). Most patients across both kinds of surgeries experienced increased taste sensitivity for sweet foods, with higher rates of this reported at 6 months (50%) as compared to at 3 months (75%) following SG surgery. However, while among GB patients the rate was higher at 3 months (58%), this decreased at 6 months (42%).

Body weight and their association with, zinc levels among GB and SG patients during follow-up were provided in *table 4.2.* Participants experienced only minor changes in responses to salt and sour tastes, with most patients reporting change experiencing an increase in salt and sour sensitivity rather than any decrease in sensitivity, as shown in *table 4a.2*.

Table 4a.2 Mean differences for weight reduction, zinc levels, taste strips and questionnaire outcomes, at 3- and 6-month follow-ups. patients subject to sleeve gastrectomy (SG) and gastric bypass (GB).

	3 MONTHS			6 MONTHS		
	SG (n=25)	**GB (n=18)**	**Diff.†**	**SG (n=20)**	**GB (n=17)**	**Diff.**
BMI reduction kg/m^2,mean(SD)	8.52 (5.9)	4.35 (3.4)	0.01	10.9 (5.7)	6.0 (3.8)	0.005
Body weight reduction kg, mean(SD)	20.8 (7.1)	13.4 (7.1)	0.001	30.6 (16.1)	17.9 (8.8)	0.006
Zinc mg/dl, mean(SD)	73.8 (15.7)	70.7 (14.43)	0.51	84.9 (21.6)	67.5(9.16)	0.004
Questionnaire elements n (%)						
Appetite change, n (%)	18/25 (72.0)	13/18 (72)	0.98	17/20 (85)	10/16 (63)	0.15
Taste change, n (%)	9/25 (36.0)	13/18 (72)	0.03	9/20 (45)	9/16 (56)	0.74
Smell change, n (%)	4/24 (16.6)	4/18 (22)	0.70	3/20 (15)	4/16 (25)	0.68
Overall loss of taste, n (%)	2/25 (8.0)	6/18 (33)	0.05	2/20 (10)	5/16 (31)	0.20
Increased taste to sweet foods, n (%)	6/8 (75.0)	7/12 (58)	0.64	7/14 (50)	3/7 (42)	0.99
Decreased taste to sweet foods, n (%)	2/8 (25.0)	6/12 (50)	0.37	2/14 (14)	2/7 (29)	0.57
Increased taste to salty foods, n (%)	4/8 (50.0)	4/11 (36)	0.65	1/12 (8)	0/6 (0)	-
Decreased taste to salty foods, n (%)	0/8 (0.0)	2/11 (18)	-	2/13 (15)	1/6 (17)	0.99
Increase taste to sour foods, n (%)	4/8 (50.0)	3/10 (30)	0.63	3/13 (23)	2/6 (33)	0.99
Decreased taste to sour foods, n (%)	1/8 (13.0)	4/10 (40)	0.31	3/13 (23)	0/6 (0)	-
Taste Strips outcomes						
Overall hypogeusia, n (%)	9/25 (36.0)	8/18 (44.4)	0.75	2/19 (11.0)	7/16 (44.0)	0.052
Sweet hypogeusia, n (%)	6/25 (24.0)	6/18 (33.3)	0.51	2/19 (11.0)	2/16 (12.5)	0.86
Sour hypogeusia, n (%)	4/25 (16.0)	5/18 (27.8)	0.45	3/19 (15.8)	5/16 (31.3)	0.42
Salt hypogeusia, n (%)	5/25 (20.0)	6/18 (33.3)	0.48	4/19 (21.1)	4/16 (25)	0.78
Bitter hypogeusia, n (%)	3/25 (12.0)	0/18 (0.0)	-	0 /19 (0.0)	0/16 (0)	-

† The test for a difference was performed using an independent t-test for parametric variables; Person Chi-square was used for the difference in proportions, P-value of 0.05. While † Fisher's exact test for low expected frequencies was used for the taste change questionnaire outcome (i.e. 20% of the expected frequencies at < 5), P-value of 0.05. † Fisher's exact test was also used for the outcomes of the taste strips test to illustrate the % of overall hypogeusia and % of hypogeusia in each taste quality during the follow-up period, among patients who underwent sleeve gastrectomy and gastric bypass.

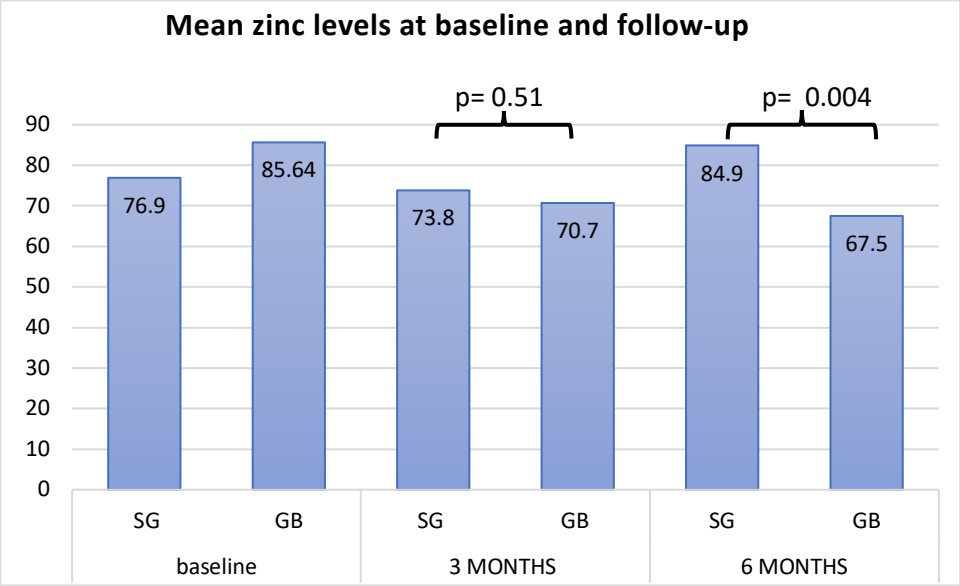


Figure 4a.1 Mean zinc levels change at baseline and follow-up.

A notable decline in zinc levels was seen following SG (n=25) over the 3-month follow-up period, in comparison to the baseline measurements (73.8±15.7 vs. 76.90±11.41). Likewise, a notable reduction in zinc concentrations was seen following GB (n=18) surgery throughout the 3-month follow-up period, as compared to the initial measurements (70.7±14.4 vs. 85.64±17.0). At the six-month mark, there was an observed rise in zinc levels among patients in the SG (n=20) group (mean: 84.9±21.6), whereas patients in the GB (n=17) group had a further reduction in zinc levels (mean: 67.5±9.16).

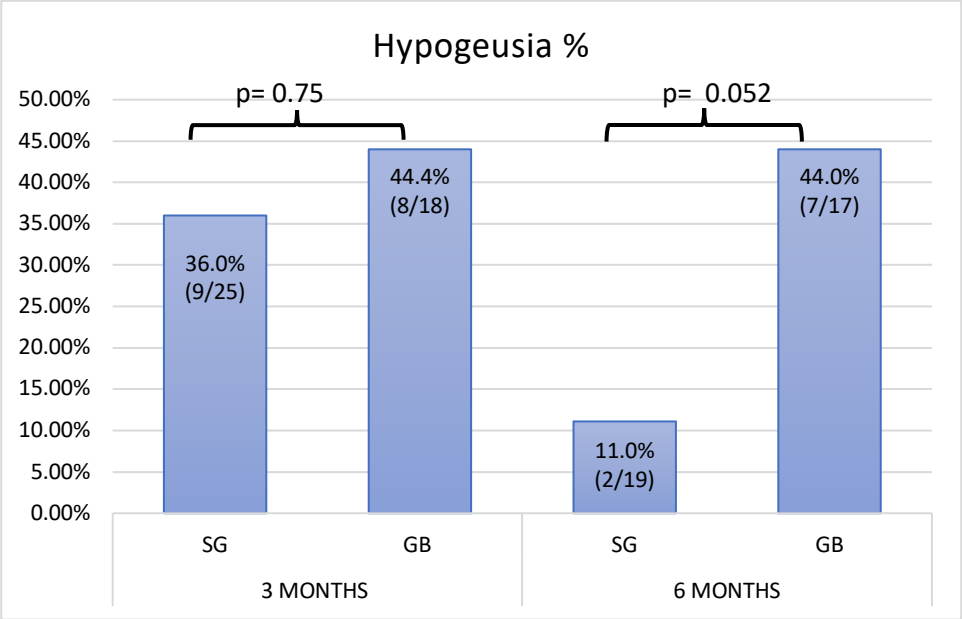


Figure 4a.2 The prevalence of overall hypogeusia among SG and GB patients.

At 3 and 6 months, the prevalence of hypogeusia among patients underwent GB; n=18, was higher than SG; n=25, the percentage of hypogeusia among SG patients decreased significantly at 6 months comparing to 3 months.

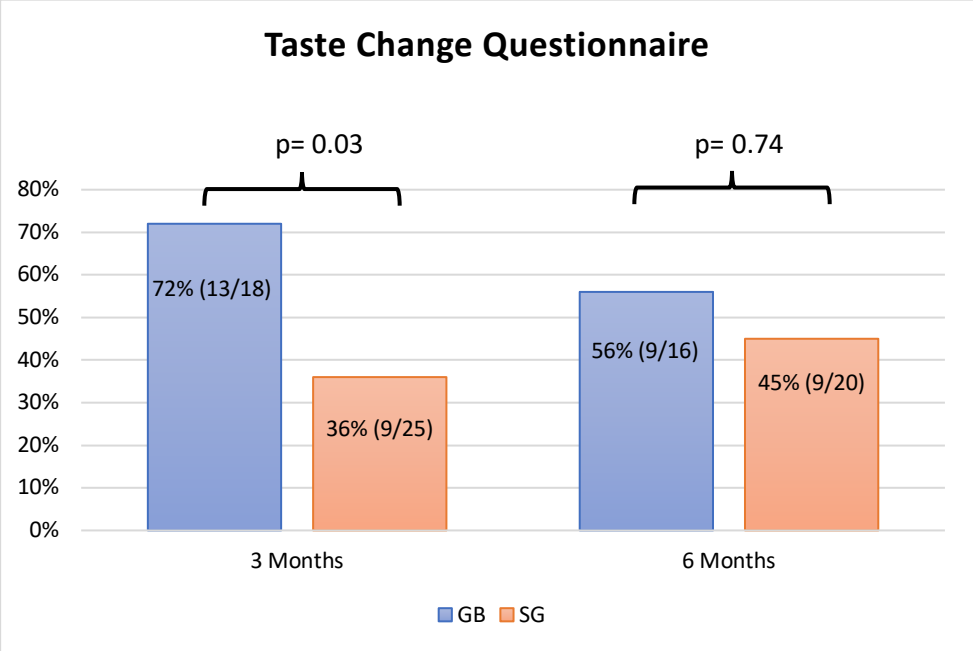


Figure 4a.3 The prevalence of taste change among SG and GB patients.

At 3 and 6 months, the prevalence of taste change among patients underwent GB; n=18, was higher than SG; n=25.

4a.5.3 Correlation between taste and zinc:

No formal correlation between zinc deficiency and taste change was established during testing.

4a.5.4 Salivary flow rate

Table 4a.3 Mean salivary flow rates and zinc levels among sleeve gastrectomy and gastric bypass patients during the follow-up period.

	Gastric bypass (N=18)		**Sleeve gastrectomy (N=25)**	
	3 months n=18	**6 months n=17**	**3 months n=25**	**6 months n=20**
Salivary flow rate ml/min mean (SD)	4.63 (3.03)	4.91 (2.67)	4.44 (2.84)	4.79 (3.52)
Salivary flow rate (low and very low), %	12 (66%)	8 (47%)	18 (72%)	14 (70%)

Results in *table 4a.3* show that the mean salivary flow rate after both types of surgeries is below the normal range; while the salivary flow rates slightly increased at 6 months 4.79±3.52 for SG and 4.91±2.67 GB as compared to those reported at 3 months 4.44±2.84 for SG and 4.63±3.03 for GB, these remained below the normal range. Zinc values were decreased at 3 months post-SG surgery, though these increased to normal levels at the 6-month follow-up. GB patients, however, experienced continuous reductions in zinc levels, which remained below normal values up to 6 months post-surgery. This tends to support a potential association between decreased zinc levels and decreased salivary flow rates among bariatric patients.

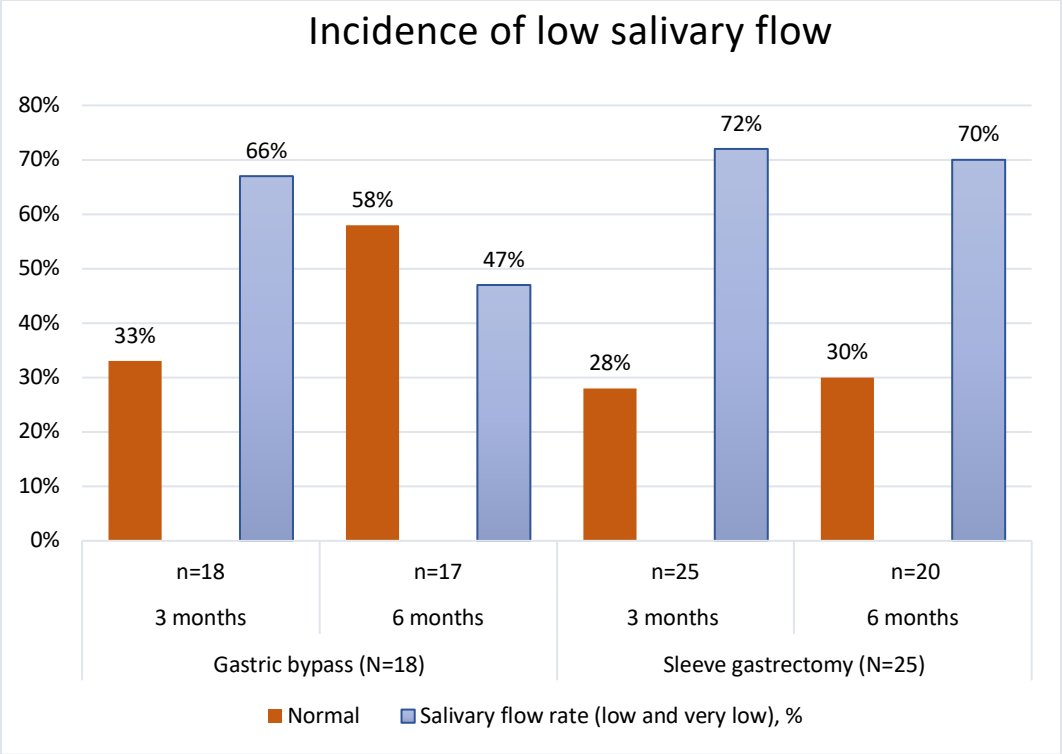


Figure 4a.4. Incidence of low salivary flow rate among SG and GB patients.

The salivary flow rate following both types of operations (SG; n=25, GB; n=18) is seen to be lower than the standard range. However, there is a little rise in salivary flow rates at 6 months, with values of 4.79±3.52 for SG and 4.91±2.67 for GB, compared to the values reported at 3 months, which were 4.44±2.84 for SG and 4.63±3.03 for GB. Despite this increase, the salivary flow rates at both time points remained below the normal range.

4a.6 Discussion

Unlike the reports from other studies, the results from the survey agreed with taste strip outcomes in this research, with a considerable percentage of patients reporting hypogeusia in the survey that were confirmed using the taste strip test. The results from the questionnaire showed that the prevalence of taste change among SG patients was higher at 6 months, at 45% than at 3 months following surgery, 36%; however, after GB surgery, the percentage was high at 3 months, 72%, decreasing to 56% at 6-months post-surgery. A comparison between the two types of surgery at 3 and 6 months showed notable alterations in taste perception, affecting some flavour categories such as sweet, salty, and sour, as well as other taste domains. The results showed that hypogeusia was higher among GB patients than SG patients. These results indicate that hypogeusia is a frequent side effect after both types of BS while being more frequent among GB patients. These results are thus in agreement with a recent review that found that taste change was reported more frequently among GB patents than those undergoing other types of BS [305]. This study also used a taste strip test to compare the outcomes after both methods of surgery: these tests confirmed that hypogeusia was more frequent after GB than after SG: at 6 months post-surgery, the rates of hypogeusia were 44.00% among GB and 11% among SG patients. The results from previous studies that used surveys to examine taste changes following BS were thus in agreement with this. Graham et al. (2014), for example, found that 75% of GB patients reported taste changes [280], while Tichansky et al. [282] found that 82% of GB patients reported decreased intensity of taste.

No studies using patient self-reports contradicted this idea of taste change following BS, though controversy has arisen based on variance in detecting taste changes using

quantitative or experimental methods such as taste detection and recognition thresholds. A recent review suggested that findings from studies are dependent on the methodologies employed to measure taste alteration. For example, while survey research sees patients regularly reporting changed tastes after BS, commonly 6 months after surgery, research using experimental techniques to investigate taste alterations, such as recognition thresholds, fMRI, and the sweetness acceptability test, have not generally discovered any appreciable rate of change in taste after BS [305]. The experimental results in this study thus disagreed with previous experimental studies that did not detect any change in taste: in this work, a considerable number of participants demonstrated hypogeusia based on the taste strips examination test. Of note, all GB patients in our study underwent SG for at least 4 years before GB. However, this may not cause a huge impact in taste change among GB patients as previous studies have shown that taste change is less common among SG patients comparing to GB [135]. Studies into long-term follow-up of taste change following BS is very limited. There was also a significant reduction in mean zinc levels among GB patients from baseline and after 6 months, despite multivitamin supplementation being taken by patients every day. In this study, the surgeons prescribed centrum supplementation for at least 6 months following sleeve gastrectomy operations, and for life after GB surgeries. However, the single tablet serving for this supplement contains only 5 mg of zinc, an amount significantly less than the recommended daily intake according to the British Obesity and Metabolic Surgery Society (BOMSS, 2020), which suggests that zinc should be consumed at a ratio of 8 to 15 mg per mg of copper [73]. Currently, no study has previously investigated dosage of zinc supplementation and its effect on taste change in GB patients. We did not examine patients' compliance to multivitamins supplements. The maximum daily zinc consumption that is unlikely to have a negative

impact on health is 40 mg for those over 19 years of age [309], and the role of zinc in the support of taste and the development of taste buds has been well established in the previous literature [310, 311]. These facts, taken together, suggest that the current zinc supplementation prescribed in clinical practice is insufficient to avoid zinc deficiency and thus to help prevent taste change following GB.

This study supports further investigation into a possible link between decreased zinc levels and hypogeusia following BS due to the clear zinc level reductions in the first 6 months following GB that may be potential associated with hypogeusia and overall taste change among participants. The most interesting finding from this study may be, however, that the percentage of hypogeusia, while high among SG patients at 3 months, significantly decreased in SG patients at 6 months post-surgery, a move that appears to parallel the increase in zinc levels seen in such patients during the same period. Similarly, the continuous decrease in the sense of taste at 3 and 6 months after GB appears to be associated with persistence in a decreased zinc level, further supporting zinc level as an important determinant of hypogeusia.

The higher prevalence of taste change among GB patients may thus be explained by the reduction in the intestinal absorption of consumed food by disabling up to 90% of the stomach, leading to the consumption of less food and the deactivation of the portion of the intestine where sugar and fat are mainly ingested [312]. While zinc is absorbed throughout the entire small intestine, this occurs mainly in the duodenum and jejunum [313]. Gastric bypass procedures connect the small stomach pouch with the middle small intestine, bypassing the majority of the stomach, the entire duodenum and part of the jejunum; clearly, this is likely to affect zinc absorption [312].

To the best of the author's knowledge, this is the first clinical study examining the possible relationship between decreased circulating zinc and taste changes following BS. The majority of patients receiving both types of surgeries experienced an increase in sweet taste intensity, with the incidence of this being higher at 3 months (75%) than at 6 months (50%) after SG surgery. However, among GB patients, while the incidence of this was higher at 3 months post-surgery (58%), this was decreased at 6 months (42%). The precise cause of this increase in sweet taste intensity also remains unclear, and this is thus a key topic for further research. However, the fact that taste buds can only detect flavours within moisture may make a difference here: those with dry tongues cannot taste dry substance, while increased viscosity reduces taste sensitivity [170]. Salivary issues might thus be another cause of taste change following BS. The study findings did suggest that more than half of the study participants experienced low to very low salivary flow rates after both types of BS, results which disagree with a recent systematic review and meta-analysis that evaluated salivary flow changes after bariatric surgery. That work found no significant alteration in salivary flow rates up to 24 months after BS [314]. In this case, however, the rate of affected patients was higher at 3 months post-surgery, slightly decreasing at 6 months; this further coincided with the decrease in zinc levels. Zinc plays an important role in both developing taste buds and increasing salivary flow, and it is thus suggested that reduced zinc levels following BS may cause a reduction in salivary flow secretions that further promote hypogeusia or taste change. The hypogeusia variable in this study is categorical so correlation testing did not demonstrate any formal association between zinc deficiency and taste alteration.

4a.6.1 Study strengths and limitations

This is the first clinical study to examine the potential link between zinc deficiency, taste change, and reduced salivary flow following bariatric surgery. Most GB patients in the study had SG surgery at least four years before their GB, however, this may explain the increase in % EWL among SG as compared to GB patients. Some limitations need to be highlighted. Importantly, this study was conducted throughout the Covid-19 pandemic, and taste change in some patients may thus have been affected by Covid symptoms. However, patient was tested for Covid using PCR before BS to ensure patient did not have Covid during their surgeries. Additional functional methods to assess taste change would have improved the sensitivity and specificity of our study findings. This study was only conducted in a single centre and hence findings may not able to be generalised to all clinical settings.

In this study the other medical history (for example, type 2 diabetes mellitus, infection and nerve damage) were not evaluated which might impact on food intake regulation or malabsorption. We did not apply the questionnaire and taste strips at baseline (before surgery) as we assumed that patients have normal taste, our study design is similar to other studies in the same field [280, 282, 285].

4a.7 Conclusion

Zinc levels among GB patients were lower than the normal range at both 3- and 6-months post-BS, as well as being lower than the normal range at 3 months post-SG. Taste ability improved among SG patients when zinc levels improved to the normal range, while % of hypogeusia remained high among GB patients associated with low levels of zinc.

Both methods used to assess taste change confirmed the presence of taste change following BS. Some evidence of a potential association between a reduction in zinc levels and both taste change and reduced salivary flow has also emerged, based on the fact that taste change is more prevalent among GB than SG patients. More than half of patients across both surgery types had low to very low salivary flow rates which may also contribute to the high prevalence of hypogeusia post-BS.

Having investigated the link between taste change and zinc deficiency and established the high prevalence of zinc deficiency following different types of bariatric surgery, further multi-centre study will be required with longer-term follow up to determine the relationship between zinc, hypogeusia and GB patients.

Following this, a further common adverse effect of BS is hair loss, which has tenuous links to zinc deficiency. The next chapter will explore the link between hair loss and decreased circulating zinc levels following BS.

Chapter 4b: Serum Zinc Levels as a Predictor Value of Hair Loss Following Sleeve Gastrectomy and Gastric Bypass (a Prospective Cohort Study)

Chapter Overview

Hair loss is another known side effect among post-BS patients, which may be influenced by decreased circulating zinc level. Nonetheless, minimal research has been conducted to examine the possible link between the two. Recently, this in-depth study is the first study to identify the possible link between hair loss and decreased circulating zinc level after sleeve gastrectomy and gastric bypass surgery among males and females. Moreover, the evidence for the incidence of hair loss is limited. So, this study provided some data regarding the number of people who experience hair loss in both genders. It is intended to provide multi-disciplinary bariatric teams and patients with recommendations for future research and practice. This work has been submitted for publication in the journal of *Obesity Surgery.*

4b.1 Abstract

Introduction: Hair loss is a common adverse effect that individuals report following bariatric surgery (BS). This study aims to determine the incidence of hair loss after two types of BS procedures and its link with circulating zinc level.

Methods: This is a single-centred prospective observational study that was conducted at King Abdullah Medical City, Makkah, Saudi Arabia. 43 adult patients who underwent BS intervention involving either SG (N=25) or GB (N=18) were recruited. The total follow-up period was six months. This study evaluated hair loss by asking patients whether they experienced severe, moderate, mild or no hair loss following SG and GB and measured their serum zinc levels.

Results: The incidence of hair loss among GB patients was twice that of SG patients, 66.6% vs. 32% at three months following surgery with a significant difference between the two groups ($P = 0.025$). At six months, the percentage among GB patients had increased to 75% and decreased among SG patients to 20%. A higher incidence of hair loss with GB is associated with a greater reduction in zinc levels (70.7 ± 14.43) at three months of GB surgery compared to SG (73.8 ±15.7). At six months, zinc levels decreased more among GB patients (67.5 ±9.2) and increased in SG patients (84.9 ±21.7) compared to at 3 months.

Conclusion: Hair loss is a common side effect following both types of BS procedure, with significantly higher incidence associated with lower serum zinc levels.

4b.2 Highlights

- The prevalence of hair loss among GB patients was twice that of SG patients, 66.6% vs. 32% at three months following surgery with a significant difference between the two groups (P = 0.025).
- At six months following surgery, the prevalence of hair loss among GB patients were more than that for SG patients, 75.0% vs 25.0%.
- Mean reduction in zinc levels was higher among GB patients (70.7± 14.4) at three months compared to SG patients (73.8±15.7). At six months, zinc levels decreased more among GB patients (67.5 ± 9.2) and increased in SG patients (84.9 ± 21.7).

4b.3 Introduction

Hair loss, medically known as alopecia occurs due to a disruption in the natural hair growth cycle inside the human body and can manifest in several regions of the body, with the scalp being the most frequently affected area. The scalp typically possesses over 100,000 hairs that undergo cyclic phases of growth, rest, shedding and regeneration [315]. Certain types of stress can increase levels of hair loss, such as major surgery, hormonal changes, iron or zinc deficiency, poor protein consumption, rapid weight loss and some drugs [316].

Hair loss is a common adverse effect following bariatric surgery (BS). A recent systematic review and meta-analysis found that the prevalence of hair loss after BS was 57% [317]. The most common types of BS worldwide are RYGB and SG [241]. Although highly effective in treating weight loss and obesity, both types of BS can lead to many nutritional deficiencies which can lead to concomitant systematic and neurological abnormalities [72]. The most common vitamin and mineral deficiencies following BS are vitamin B12, thiamine, folic acid, A, D and K [318], while zinc insufficiency has been shown to continue to be present for up to 60 months following surgery in patients who underwent SG (12.5%), GB (21-33%) and biliopancreatic diversion (45%) [319].

There are many factors which leads to hair loss such as genetic causes, vitamin and mineral deficiencies, drug usage, stress and depression, skin issues, hair growth abnormalities, poor nutrition, hormone issues, and the chemotherapy process [320]. Deficiencies in zinc have also been linked to hair loss [80], [73]. Despite appropriate multivitamins and mineral supplementation, many patients can still suffer hair loss

[321]. To avoid and minimise post-BS hair loss, many individuals consult their bariatric MDT and/ or bariatric patients' online forums and support groups to learn about further hair treatments. These may consist of nutritional supplements and shampoos containing biotin, protein, zinc or selenium [322].

This study aims to identify the possible link between zinc and hair loss following BS and the incidence of hair loss following BS. The study intends to inform both bariatric MDTs and patients who have BS, as well as provide recommendations for future practice and research.

4b.4 Methods

As described in Chapter 3.

4b.5 Results

The prevalence of postoperative hair loss for both types of surgery

At three months after SG, most SG patients (n= 17; 68.0%) had not experienced hair loss, however, most GB patients reported hair loss (12; 66.6%). For the later, with the exception of one male, the rest of these patients were female with a decrease in serum zinc levels reported in nine patients who had zinc levels below 70 mg/dl. Meanwhile, patients who had mild to no hair loss had zinc levels higher than 70 mg/dl, all of whom were male (n=5) except one female. For the SG group, eight patients out of 25 had experienced severe hair loss, all of these were female and most of them had a zinc level below 70 mg/dl (N=6). The remaining 17 patients had experienced mild hair loss, 10 of whom had zinc levels higher than 70 mg/dl.

The Pearson chi2 test (1) = 5.0553 indicated a significant difference between the two groups (P = 0.025). Therefore, GB patients were more affected by hair loss at three months following surgery compared to SG patients. (Table 4b.1)

At six months following surgery, the prevalence of hair loss among GB patients (12; 75.0%) was more than that for SG patients (4; 25.0%). Among GB patients, of the 12 patients who experienced severe hair loss, 10 were female. Decreased serum zinc levels were found in 10 patients who had zinc levels below 70 mg/dl. The four patients (three male and one female) who experienced mild hair loss had a zinc level below 70 mg/dl. For the SG group, four patients out of 20 had experienced severe hair loss. Sixteen patients who reported mild to no hair loss, showed a non-significant change in zinc level. The results also showed that there is a significant difference between groups in terms of hair loss Pearson chi2(1) = 10.8900 (P = 0.001). (Table 4b.1)

Table 4b.1 The prevalence of hair loss for both types of surgery

Type of surgery	**No hair loss**	**Presence of hair loss**
3 MONTHS		
SG/ n= (25)	17 (68.0%)	8 (32%)
GB/ n= (18)	6 (33.3%)	12 (66.6%)
6 MONTHS		
SG/ n= (20)	16 (80.0%)	4 (20.0%)
GB / n= (16)	4 (25.0%)	12 (75.0%)

The prevalence of zinc deficiency in patients for both types of surgery

Table 4b.2 Zinc levels in patients after sleeve gastrectomy and gastric bypass.

	Sleeve gastrectomy (N=25)	Gastric bypass (N=18)	Diff.
Baseline	76.90 ±11.41	85.6±16.9	-
3 months	73.8± 15.7	70.7± 14.43	0.51
6 months	84.9± 21.6	67.5± 9.16	0.004

The results showed that the mean reduction in zinc levels was higher among GB patients (70.7± 14.4) at three months compared to SG patients (73.8±15.7). At six months, zinc levels decreased more among GB patients (67.5 ± 9.2) and increased in SG patients (84.9 ± 21.7).

Correlation of Hair Loss with zinc deficiency

A correlation test between hair loss and zinc deficiency could not be established.

4b.6 Discussion

Hair loss is a common side effect following BS. However, studies regarding the incidence of hair loss following SG and GB and associated causes and factors are lacking. Micronutrient deficiencies are known to increase the chance of developing hair loss. The determination of serum zinc levels in patients with hair loss and the assessment of zinc supplementation as a therapeutic factor are the subject of recent research. The present study provides data about the prevalence of hair loss among SG and GB patients and serum zinc levels among those patients at baseline and up to six months post-bariatric surgery.

Summary of main results

This study's results showed that the percentage of the prevalence of hair loss among GB patients was twice that of SG patients, 66.6% vs. 32% at three months following surgery with a significant difference between the two groups (P = 0.025). At six months, the percentage increased among GB patients to 75% and decreased among SG patients to 20% with a significant difference between groups (P = 0.001). At three months, serum zinc levels among GB patients were lower than SG patients and at six months, this improved to reach normal levels but decreased more among GB patients with a significant difference between the two groups (P= 0.004).

The results of the present study are in agreement with a recent systematic review and meta-analysis which found that the prevalence of hair loss among metabolic and bariatric surgery was 57% and more common among patients with low serum zinc levels [317]. Zinc is absorbed throughout the entire small intestine, but the primary site of intestinal zinc absorption in humans is still debatable. In rats, the maximum absorption rate has been reported in the duodenum and ileum. The GB procedure bypasses the duodenum (the first part of the small intestine) and a portion of the jejunum (the second part of the small intestine) and the surgeon creates a direct connection from the stomach pouch to the lower part of the small intestine, delaying the mixing of food and digestive enzymes. This may help to explain the low level of zinc among GB patients compared to SG patients despite the daily intake of multivitamins. A study found that zinc absorption decreased significantly from 32.3% to 13.6% at six months after RYGB [235]. According to BOMSS 2020, the comprehensive multivitamin and mineral supplement may not include enough zinc to avoid zinc insufficiency after SG and RYGB. The optimum level of zinc supplementation is unknown, however, BOMSS suggests starting with 15 mg of zinc. It is suggested that the current multivitamin supplementation is not enough to avoid hair loss following GB due to the decreased

absorption percentage following this procedure. This paper therefore proposes that it is necessary to increase the zinc supplement dose to avoid hair loss after GB, but the risk of a high zinc dose exceeding the recommended daily amount (RDA) when taking an excess amount between 100-300 mg Zn/d should also be considered. This study includes some limitations, the absence of baseline data regarding hair loss made it difficult to compare the changes in hair loss before and after bariatric surgery, especially as GB participants had already had SG for at least 4 years before being entered into the trial and the questionnaire for hair loss was not validated.

4b.7 Conclusion

Hair loss is a prevalent side effect following BS and is more prevalent in GB patients compared to SG patients. Zinc levels were lower than the normal range among GB patients at six months following surgery.

Taste change has an important impact on dietary compliance and eating behaviour post-BS. I will next undertake a systematic review and meta-analysis to identify the effectiveness of zinc supplementation on taste change treatment.

Chapter 5: The Effectiveness of Zinc Supplementation in Taste Disorder Treatment: A Systematic Review and Meta-analysis of Randomized Controlled Trials.

Chapter Overview

In the systematic review in chapter two, the findings indicated that zinc deficiency appears to be associated with taste change after bariatric surgery and Supplementation with much higher levels of zinc, at 45–50 mg, was effective in taste change treatment for many cases of taste disorder. So, I used these findings to develop the protocol in Chapter Three, followed by the study 1 in Chapter Four prospective cohort study that investigates the association between taste and zinc after BS. Therefore, in this chapter, I performed a systematic review and meta-analysis of only RCT studies to investigate the effective doses of zinc supplementation in taste disorder treatment regardless of BS. Which will inform future studies in this field. The findings of this chapter were published in the *Journal of Nutrition and Metabolism.*

5.1 Abstract

***Introduction*:** Food taste and flavour affect food choice and acceptance, which are essential to maintaining good health and quality of life. Reduced circulating zinc levels have been shown to adversely affect the taste, but the efficacy of zinc supplementation to treat disorders of taste remains unclear. In this systematic review and meta-analysis, we aimed to examine the efficacy of zinc supplementation in the treatment of taste disorders.

***Methods*.** We searched four electronic bibliographical databases: Ovid MEDLINE, Ovid Embase, Ovid AMAD, and PubMed. Article bibliographies were also searched, which yielded additional relevant studies. There were no restrictions on the publication date to facilitate the collection and identification of all available and relevant articles published before 7 February 2021. We performed a systematic review and meta-analysis according to the PRISMA Statement. This review was registered at PROSPERO and given the identification number CRD42021228461.

***Results*.** In total, we included 12 randomized controlled trials with 938 subjects. The intervention includes zinc (sulfate, gluconate, picolinate, polaprezinc, and acetate), and the pooled results of the meta-analysis of subjects with idiopathic and zinc-deficient taste disorder indicate that improvements in taste disorder occurred more frequently in the experimental group compared to the control group (RR = 1.38; 95% CI: 1.16, 1.64). Zinc supplementation appears to confer a greater improvement in taste perception amongst those with chronic renal disease using zinc acetate (overall RR = 26.69, 95% CI = 5.52–129.06). The doses are equivalent to 17 mg–86.7 mg of elemental zinc for three to six months.

***Conclusion*.** Zinc supplementation is an effective treatment for taste disorders in patients with zinc deficiency, idiopathic taste disorders, and in patients with taste

disorders induced by chronic renal failure when given in high doses ranging from 68 to 86.7 mg/d for up to six months.

5.2 Introduction

Food taste and flavour are important elements that affect food choice and acceptance [323]. Disorders of taste can adversely affect patients' health and quality of life [324] through loss of food enjoyment, poor appetite, unintended weight loss, malnutrition and other psychological and physiological complications [325-327]. Taste disorder is characterised by unpleasant tastes, where patients can experience hypogeusia, (a condition of reduced ability to taste sweet, sour, bitter, salty and umami tastes) or ageusia (a total loss of the ability to detect tastes), or dysgeusia, (persistent foul, salty, rancid or metallic taste sensation in the mouth) [328]. Around 200,000 patients visit doctors each year in the US complaining of a change in either taste or smell [323]. In 2003, about 240,000 patients were diagnosed with taste disorders in Japan [324]. A recent US survey using the Chemical Senses Questionnaire (CSQ) reported that the prevalence of taste alteration was 19% in the adult population, with 5% reporting dysgeusia. This percentage increased with age to reach 27% in elderly populations [329]. More than half of patients (56.9%) in Italy with COVID-19 have reported a reduction of taste and/or smell; a severe reduction of taste was present in 39.7% of patients [330]. Taste alteration is also observed in 66% of chemotherapy patients [331]. The most common causes of taste disorder are medications (21.7%) followed by zinc deficiency (14.5%), oral and perioral infections, Bell's palsy, oral appliances and age while less common causes include nutritional factors, tumours or lesions associated with taste pathways, head trauma, exposure to toxic chemicals and radiation treatment of the head and neck [332].

Zinc is an important element that supports many functions in humans including the immune system, growth and development [79]. In addition, zinc is important for the functioning of taste buds [311]. Disturbance of salivary zinc levels is associated with a decreased level of Gustin [333]. Gustin is the major zinc-containing protein in the human parotid saliva [311]; decreases in the secretion of Gustin have been linked with abnormalities of the growth and development of the taste buds and resultant loss of taste [334]. This mechanism is supported by numerous studies finding that hypogeusia patients had low levels of Gustin and salivary zinc [334-336] as well as a severe change in the shape of taste buds [335]. The association between zinc deficiency and taste disorders has been well known for years [259, 337, 338], but evidence for efficacious treatment for taste disorders in clinical practice remains lacking. Although taste disorder has not been given sufficient attention by the medical community and researchers, in recent years, increased interest has emerged in evaluating potential treatments for disorders of taste due to the increasingly recognised adverse effect of taste as a result of bariatric surgery [339] and most recently due to COVID-19 infections [340]. We, therefore, aim to perform a systematic literature review and meta-analysis for available randomized controlled trials to investigate the efficacy of zinc supplementation in the treatment of taste disorders in the adult population.

5.3 Methods

We performed our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [341] to identify the effectiveness of zinc supplementation to prevent and treat taste disorder in patients who had been diagnosed with zinc deficiency, idiopathic taste disorder or taste disorder secondary to chronic renal failure. Included and excluded studies were assessed based on outcomes, participants, intervention types and study types.

5.3.1 Inclusion and exclusion criteria

5.3.1.1 Study types

We only included randomized control trials; all other study designs were excluded.

5.3.1.2 Participants

All included participants consisted of human populations, animal studies were excluded. Participant groups consisting of adults ≥18 years were included. We excluded patients who received chemotherapy and radiation, children and pregnant women. We also excluded patients with taste disorders induced by drug use or taste disorders induced by the common cold.

5.3.1.3 Intervention

The participants received zinc-based therapy for the prevention and treatment of taste disorders compared to controls who received a placebo.

5.3.1.4 Outcomes

Improvement of taste disorder in response to zinc treatment was observed in intervention groups compared to the control group at the baseline and during a follow-

up period. Zinc levels were also compared before and after treatment. Papers that did not include zinc or taste change outcomes were excluded.

5.3.2 Search strategy

A literature search was conducted to describe the effects of zinc supplementation on improving subjective and objective symptoms of taste disorder induced by zinc deficiency, idiopathic conditions or chronic renal failure. Two authors conducted the systematic search in the following electronic bibliographical databases: Ovid MEDLINE, Ovid Embase, Ovid AMAD and PubMed. Article bibliographies were also searched and yielded additional relevant studies. There were no restrictions on publication date, facilitating the collection and identification of all available and relevant articles published before 7 February 2021. The following keywords were used: taste change, taste disorder, Zn deficiency, Zn supplementation, Zinc sulphate. The systematic review was registered at PROSPERO (https://www.crd.york.ac.uk) and given the identification number CRD42021228461.

5.3.3 Data extraction

We reviewed the articles according to the inclusion and exclusion criteria and summarised the main findings. Data regarding study duration, sample size, methods of detection of taste disorder, zinc dose, treatment period and outcomes were extracted and are summarised in *table 6.1* and *table 6.2.* All data utilised for the meta-analysis component was dichotomous data to find out the number of events in both intervention and placebo groups. Additionally, all zinc supplement doses were considered for meta-analysis implementation.

Table 5.1 The main patient characteristics of the included studies.

Author(s), year and (study duration)	Country	Study type	Total no. of patients	No. of patients receiving zinc	No. of patients receiving placebo	Gender	Age (year)	Zinc supplement	Disease or case-induced taste disorder
Ikeda et al. 2013 [342] (12 weeks)	Japan	Double-blind RCT w/placebo	219	108	111	87 M & 132 F	Average for intervention: 43.3 Control: 47.1	Polaprezinc, 34mg/d	Zinc deficiency and idiopathic taste disorder
Sakagami et al. 2009 [267] (12 weeks)	Japan	Double-blind RCT w/placebo. Multi-centre	109	81	28	M &56 F51	20-80	Polaprezinc, (Group 1) 17 mg (n=27), (Group 2) 34 mg (n=26) or (Group 3) 68 mg (n=28) daily	Idiopathic taste disorder
Stewart-Knox et al., 2007 [260] (6 months)	Japan	Double-blind RCT w/placebo	199	NR	NR	103 M & 96 F	70-78	Zinc gluconate, Elemental zinc gluconate (Group 1) 15 mg/d and (Group 2) 30 mg/d	Idiopathic taste disorder in elderly people
Heckmann et al. 2005 [343] (3 months)	Germany	RCT w/ placebo	50	24	26	7M & 43F	41-82	Zinc gluconate (140mg/d, equivalent to 20mg/d of elemental zinc)	Idiopathic taste disorder
Matson et al. 2003 [344] (6 weeks)	UK	Double-blind RCT w/placebo	24	12	12	M & F	30 to 72	Zinc sulphate	Chronic renal failure
Sakai et al. 2002 [256] (3 months)	Japan	Double-blind RCT w/placebo	73	37	36	M/NR&47F	23-79	Picolinate, 28.9 mg of elemental zinc three times/d	Zinc deficiency & idiopathic taste disorder
Yoshida & Tomita 1991[345] (4 months)	Japan	Double-blind RCT w/placebo	52	28	24	M to F ratio was 1:1.8	Mean age for group 55.1 &59.2 for placebo	Zinc gluconate, 158 mg Zinc gluconate; zinc content: 22.59 mg	Zinc deficiency & idiopathic taste disorder
Mahajan et al. 1982 [346] (6 months)	USA	Double-blind RCT w/placebo	24	12	12	Only males	Treatment 46 ± 8 Control 49 ± 12	Zinc acetate, Zinc acetate (50 mg of elemental zinc/d)	Chronic renal failure
Mahajan et al. 1980 [347] (6 months)	USA	Double-blind RCT w/placebo	22	11	11	NR	Treatment: 51.3±3.2 Control: 55.1±2.8	Zinc acetate, Zinc acetate (50 mg of elemental zinc/d)	Chronic renal failure
Mahajan et al. 1979 [348] (6 months)	USA	Double-blind RCT w/placebo	31	11	20	NR	NR	Zinc acetate, Zinc acetate (50 mg of elemental zinc/d)	Chronic renal failure
Atkin-thor et al. 1978 [261] (6 weeks)	USA	Double-blind crossover RCT w/placebo	29	20	9	NR	21-70	Zinc sulphate, 440 mg $ZnSO_4$ Post-dialysis, 3 times per week	Chronic renal failure

Henkin et al. 1976 [349] (6 months)	USA	Double-blind crossover RCT w/placebo	106	Not clear	Not clear	53M &53F	19-84	Zinc sulphate, 100 mg of zinc ion in four oral doses	Idiopathic taste disorder

NR: not reported, M: Male, F: Female, RCT: Randomized controlled trial, w: with

Table 5. 2 Summary of the findings of the included studies

Author(s), year	Test method	Statistical analysis	Zinc level at baseline	Zinc status after treatment/intervention group	Zinc status after treatment /placebo group	Significant improvement against placebo	Taste status/ intervention group	Taste status/ placebo Group	Significant improvement against placebo
Ikeda et al. [342]	Filter paper disc method	Wilcoxon rank-sum test & fisher's exact test	71.1 µg/dl zinc group, 73.5 µg/dl placebo group	NR	NR	NR	NR	NR	NR
Sakagami et al. [267]	Filter paper disc method and serum zinc level	Shirley-Williams test & unpaired student's *t-test*, Dunnett's test, Fisher's exact test	↓ 69 µg/dl	Serum zinc level↑ 5.7 ± 13.5 (17 mg), 11.4 ± 16.6 (34 mg), and 20.6 ± 21.3 (68 mg), respectively, ($p < 0.001$), statistically significant increase in group receiving 68 mg of zinc ($p<0.001$)	1.8±12.7	($p < 0.001$) sig	The efficient rate of gustatory sensitivity was 51.9%, 80.0% and 89.3% in the 17 mg, 34 mg and 68 mg zinc-treated groups, respectively,	The efficient rate (63.0%)	$p = 0.018$ sig
Stewart-Knox et al. [260]	Detection thresholds for sweet, sour, salty, bitter and umami	Factorial ANOVA	Within normal range for placebo & zinc groups (11-18 µ mol/l)	Zinc level increased post-intervention in both groups and greater in the 30 mg group	13.05±1.66 µ mol/l	P = 0.000 sig	Acuity for salt taste was greater in the 30 mg supplemented group (0·84 409 (SD 0·13 349) 15 and 30 mg Zn did not improve any tastes acuity.	0·75 045 ± 0·210	$p = 0.031$ sig
Heckmann et al. [343]	Filter paper strips and serum zinc level	T-test for independent samples and correlation (Pearson's) test	72.78 ± 18.38 mg/dl	No significant change in serum zinc level before and after treatments. 81.53±19.61	72.01±10.22	P = 0.65 not sig	There were significant improvements in the zinc group compared to the placebo group 25.7±6.5	21.2 ± 5.7	$p < 0.001$ sig
Matson et al. [344]	Filter paper disc method, questionnaire, and serum zinc level	Unpaired *t*-test	Placebo 10.9 ± 1.1_ µ mol/l Intervention 9.9 ±1.6 µ mol/l	Intervention 10.4 ±1.4 µ mol/l	Placebo 10.5 ± 1.6 µ mol/l	NS	Not improved	Not improved	NS

Sakai et al [256]	A questionnaire, filter paper disc method and serum zinc level	Student's *t*-test and Wilcoxon's test	For zinc-deficient group≤ 69 µg/dl, Idiopathic (70 µg/dl≥	significantly greater increase in serum zinc level after treatment 81.6 µg/dl	Serum zinc level after treatment 72.3 µg/dl	$p < 0.01$ sig	There was a significant difference between groups in objective improvements in taste 28 patients improved and 9 not improved	16 improved and 20 not improved	$P < 0.01$ sig
Yoshida & Tomita [345]	Filter paper disc method and serum zinc level	Chi-square test	For zinc-deficient group, 60-69 µg/dl; for idiopathic group, 70 µg/dl or higher	Serum zinc concentration was significantly higher during the intervention period, 94.0±24.6 (n=20)	71.9 ± 10.9 (n = 23)	$p < 0.01$ sig	A significant difference was detected between the two groups in therapeutic efficiency (23 patients improved and 5 unchanged)	13 patients improved and 11 unchanged	$p < 0.05$ sig
Mahajan et al. [346]	The threshold of taste detection and recognition for salty, sweet and bitter, and serum zinc level	Paired student's *t*-test	Intervention 81 ± 8 µg/dl Placebo 82 ± 6 µg/dl	110 ± 14 µg/dl	84 ± 9 µg/dl	$p < 0.005$ sig	Improved	Not improved	$p < 0.05$ sig
Mahajan et al [347]	The threshold of taste detection and recognition for salty, sweet and bitter, and serum zinc level	Independent student's *t-test* for unpaired data	Serum zinc level in treatment group70 µg/dl, lower than the control group	The mean plasma zinc level increased significantly from 75 ± 8 to 97 ± 10 µg/dl	No change (75 ± 15 to 80 ± 15)	$p < 0.001$ sig	Significant improvement in sweet, salty, and bitter taste	Not improved	$p < 0.05$ sig
Mahajan et al. [348]	The threshold of taste detection and recognition for salty, sweet and bitter, and serum zinc level	Independent student's *t-test* for unpaired data	75.0 ± 2.0 µg/dl zinc group,	97.2 ± 3.2 µg/dl zinc group	NR	Sig	improved	Not improved	$p < 0.005$ sig
Atkin-Thor et al. [261]	The threshold of taste detection and recognition for salty, sweet and bitter, and zinc concentration in hair	NR	Zinc concentration in hair before treatment is 2(10%) where the normal range 180±4 ppm (100%)	The serum zinc level was not published in the study; however, zinc concentration in hair increased in 85% of patients.	NR	$p < 0.01$ sig	Significant improvement in taste acuity in the supplemented group by 95% of patients 6 weeks after treatment	NR	$p < 0.01$ sig
Henkin et al. [349]	The threshold of taste detection and recognition for salty, sweet and bitter measured with the total concentration of zinc and copper and a questionnaire of taste acuity	Student's *t*-test	NR	NR	NR	NR	Significant improvement in taste disorder at 3 months	NR	NR

5.3.4 Assessment of the risk of bias in selected studies

We used the Cochrane quality assessment tool to the assessed risk of bias for randomized controlled trials. The Cochrane tool, as described in the Handbook for Systematic Reviews of Interventions, evaluates the following attributes: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other forms of bias. Rating criteria include low risk of bias, high risk of bias, or unclear risk of bias [350]. The Cochrane risk-of-bias tool for randomized trials (RoB) was performed.

5.3.5 Statistical Procedures

The meta-analysis was conducted using Review Manager 5. The Mantel-Haenszel (M-H) statistical method was selected with the random effect method for dichotomous data and established the outcome measure as a total and event based on Cochrane recommendation. All pooled results were reported as relative risk (RR) and 95% confidence intervals (CI) for all individual studies, in addition to an effect size estimate (Z-statistic) and a measure of statistical significance ($p<0.05$). To distinguish between the observed effects of zinc supplementation in iatrogenic or primary zinc deficiency versus chronic renal disease, two separate forest plots were generated for each. Further, data points from all studies at the synthesis stage were included, where data pertaining to the event & total count, the equivalent quantity of elemental zinc, and the pharmaceutical name of the zinc supplement are stated. Finally, sub-analysis was performed, based on the pharmaceutical name of the zinc supplement(s) included at the quantitative synthesis stage.

5.3.6 Assessment of Heterogeneity

We followed the Cochrane Handbook for Systematic Review of Interventions guidelines to assess the heterogeneity of the studies that were generated through the associated forest plots using Review Manager 5. Using the Chi^2 test, we interpreted the heterogeneity according to I^2 statistics: 75–100% indicates considerable heterogeneity, 50–90% represents substantial heterogeneity, 30–60% represents moderate heterogeneity and 0–40% represents insignificant heterogeneity [350].

5.3.7 Summarizing and Interpreting Results

Review Manager 5 was used to conduct the meta-analysis, risk of bias assessment and the summary of the findings in *table 6.3* for each outcome included in this review. We imported the data to GRADEpro software to assess the evidence for each outcome. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to examine the publication bias on a study-specific level *table 6.4.* The statistical assessment of publication bias, meta-regression, and trial sequence analysis was not viable due to the small number of papers per area of research.

Table 5.3 Summary of Findings

Zinc supplement compared to placebo for improvement of taste disorder

Patient or population: Improvement of taste disorder
Intervention: Zinc supplement
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**The risk with zinc supplement**				
Polaprezinc supplementation in idiopathic and zinc-deficient taste disorder patients, equivalent to (17mg, 68 mg) of elemental zinc for 12 weeks.	454 per 1,000	**671 per 1,000** (535 to 839)	**RR 1.48** (1.18 to 1.85)	223 (2 RCTs)	⊕⊕⊕⊕ HIGH	Polarprezinc supplementation improved taste disorder in idiopathic and zinc-deficient patients compared with the placebo by 48%, with a CI of 18% to 85% increase in taste acuity.
Zinc gluconate supplementation in idiopathic and zinc-deficient taste disorder patients, equivalent to (20mg, 22.59mg) per day of elemental zinc for 3–4 months.	396 per 1,000	**637 per 1,000** (443 to 914)	**RR 1.61** (1.12 to 2.31)	102 (2 RCTs)	⊕⊕◯◯ LOW [a,b]	Zinc gluconate supplementation improved taste disorder in idiopathic and zinc-deficient patients compared with the placebo by 61% with a CI of 12% to 131% increase in taste acuity.
Zinc picolinate supplementation in idiopathic and zinc-deficient taste disorder patients, equivalent to (28.9 mg) of elemental zinc three times per day for 3 months.	444 per 1,000	**756 per 1,000** (502 to 1,000)	**RR 1.70** (1.13 to 2.56)	73 (1 RCT)	⊕⊕⊕◯ MODERATE [c]	Zinc picolinate supplementation improves taste disorder in idiopathic and zinc-deficient patients compared with the placebo by 70% with a CI of 13% to 156% increase in taste acuity.

Table 5.3 Summary of Findings

Zinc supplement compared to placebo for improvement of taste disorder

Patient or population: Improvement of taste disorder
Intervention: Zinc supplement
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**The risk with zinc supplement**				
Zinc acetate supplementation in patients with taste disorder induced by chronic renal failure, equivalent to (50mg) per day of elemental zinc for 6 months.	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 26.69** (5.52 to 129.06)	77 (3 RCTs)	⊕⊕◯◯ LOW [d]	Zinc acetate supplementation improved taste disorder in patients with taste disorder induced by chronic renal failure compared with the placebo by 25.69% with a CI of 452% to 128.06% increase in taste acuity.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Some concern with random sequence generation and lack of follow-up
b. Wide confidence intervals in Heckmann et al. [343]
c. Some concerns of lack of follow-up
d. Very wide confidence intervals in all three included trials

Table 5.4 A Systematic Review Meta-Analysis – GRADE score results for all studies.

Lead Author	Publication date	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication Bias
Ikeda et al. [342]	2013	⊕⊕⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕⊕	N/A*
Sakai et al. [256]	2002	⊕⊕	No CI reported	N/A	⊕⊕⊕	N/A*
Yoshida & Tomita [345]	1990	⊕⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕	N/A*
Henkin et al. [349]	1976	⊕⊕⊕	No CI reported	N/A	N/A	N/A*
Sakagami et al. [267]	2009	⊕⊕⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕⊕	N/A*
Hekmann et al. [343]	2005	⊕⊕⊕⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕	N/A*
Stewart-knox et al. [260]	2008	⊕⊕	No CI reported	N/A	N/A	N/A*
Mahajan et al. [348]	1979	⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕⊕	N/A*
Mahjan et al. [346]	1982	⊕⊕⊕⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕⊕	N/A*
Mahjan et al. [347]	1980	⊕⊕⊕⊕	No CI reported	⊕⊕⊕⊕	⊕⊕⊕⊕	N/A*
Athkin-thor et al. [261]	1978	⊕⊕	No CI reported	⊕⊕	⊕⊕	N/A*
Matson [344]	2003	⊕⊕⊕	No CI reported	⊕⊕	⊕⊕⊕⊕	N/A*

Notes. N/A-not a systematic review. N/A-not applicable, CI-confidence interval.
High: ⊕⊕⊕⊕, Moderate: ⊕⊕⊕, Low: ⊕⊕, Very Low: ⊕.

5.4 Results

5.4.1 Study selection

A PRISMA flow diagram of our literature search is shown in Fig 5.1. Up to February 2021, 137 citations were identified through database searching, and an additional 4 articles were identified using relevant paper reference lists. After duplicates were removed using Endnote Manager, 69 articles were screened and 54 records were excluded. Then, 15 full-text articles were assessed for eligibility. Complete data extraction was performed on a total of 12 articles that met the inclusion criteria. Of these studies, four were included in a qualitative synthesis and eight were included in a quantitative synthesis (meta-analysis) [351]. The characteristics of these 12 articles are shown in *table 5.1*.

5.4.2 Study characteristics

5.4.2.1 Trial settings

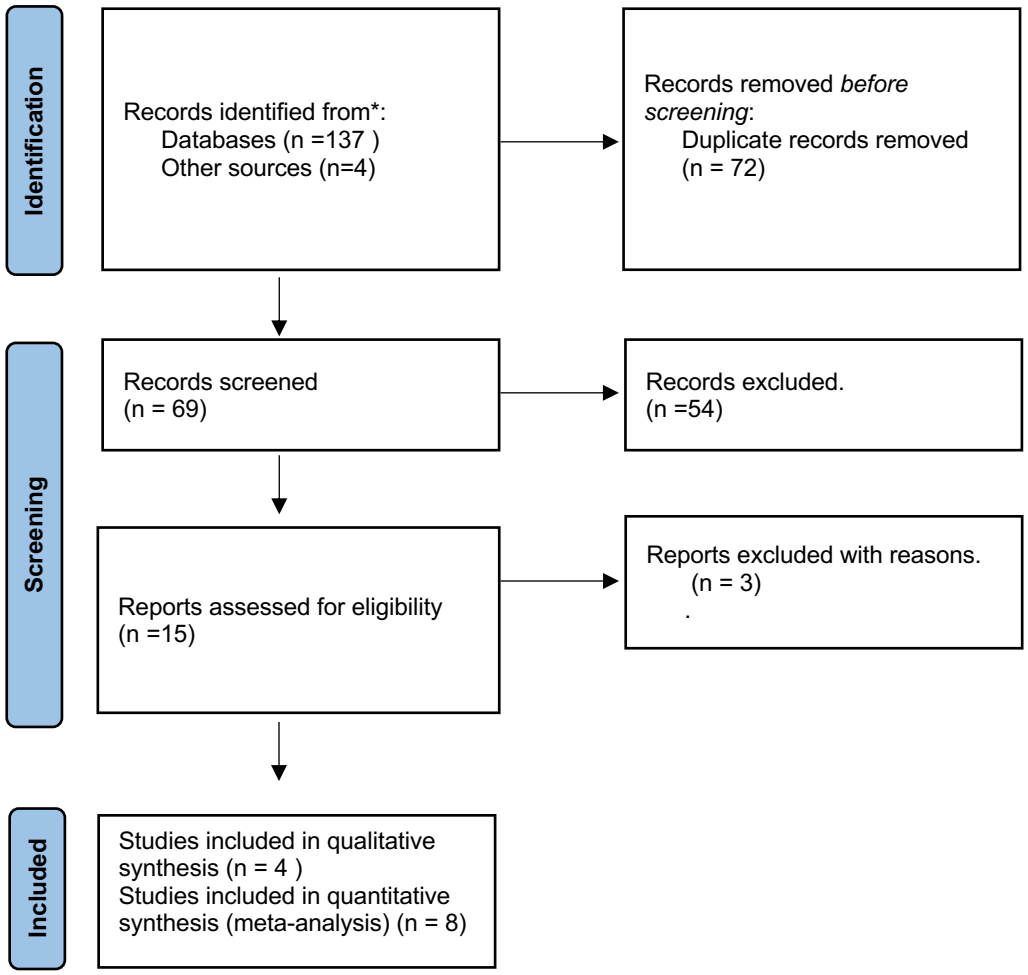
Twelve randomized controlled trials (RCTs) are included in this review; all but one were written in English. One was in Japanese but was translated into English by Ikeda et al. [342]. The most common countries of origin of these studies were Japan and the US; one was from the UK and one was from Germany. Out of 12 trials, 2 were cross-over trials.

5.4.2.2 Study populations

A total of 938 subjects were included in this study, all adults. The minimum age included in the trials was 18 years or older and the highest age observed was 84 years old; the lowest sample size was 22 and the highest sample size was 219. Eight studies included both genders in their trials; one study included only males and three trials did

not report gender distribution. Four studies were on idiopathic taste disorder, three concerned idiopathic and zinc-deficient taste disorder and five were on renal failure-induced taste disorder.

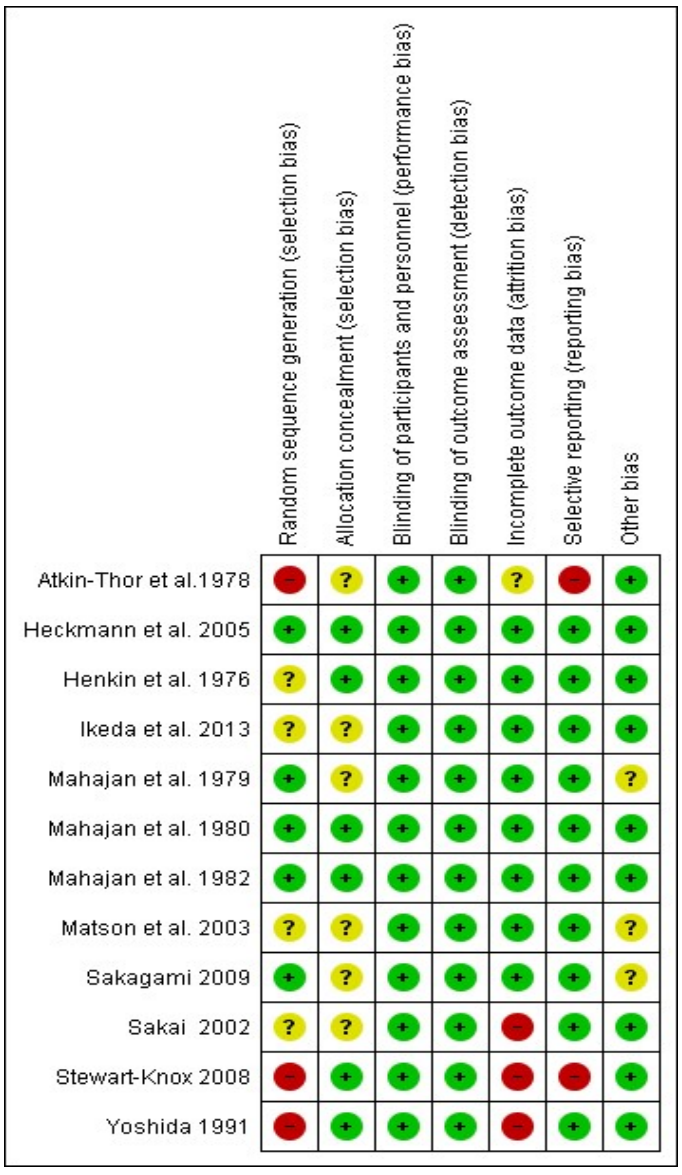
Figure 5.1 PRISMA flow diagram of the study selection and identification process.



5.4.3 Risk of bias in included studies.

Most studies were found to have an unclear risk of bias. However, four studies have a high risk of bias, and three studies have a low risk of bias. As only seven data points from four studies were incorporated for analysis, publication bias assessment was infeasible in an updated version.

Figure 5.2 Risk of bias assessment.



5.4.4 Intervention and Duration

5.4.4.1 Idiopathic and Zinc-Deficient Taste Disorder

(1) Polaprezinc. First, we evaluated the efficacy of polaprezinc supplementation in idiopathic and zinc-deficient taste disorders. The efficacy of polaprezinc was examined in two studies, using different dosages. Sakagami et al. [267]. Introduced three different dosages to the intervention group: 75 mg, 150 mg, and 300 mg, which are equivalent to 17 mg, 34 mg, and 68 mg of elemental zinc. Despite the utilisation of identical doses (17 mg), Ikeda et al. [352] and Sakagami et al. [267] presented with differing outcomes (RR = 1.54, 95% CI = 1.12–2.12, and RR = 0.81, 95% = 0.51–1.27, respectively) *Figure 5.3* . Nonetheless, across the Polaprezinc subgroup data points from Sakagami et al. [267], an increase in effect size is observed *Figure 5.3*. Although an overall supplement-specific RR is positive (RR = 1.26, 95% CI = 1.00–1.60), statistical significance was found to be borderline (P=0.05*) Figure 5.3*.

(2) Zinc Gluconate. Three trials studied the efficacy of zinc gluconate supplementation in idiopathic and zinc-deficient taste disorders. Yoshida et al.[345] administered 158 mg of zinc gluconate (equivalent to 22.59 mg/d of elemental zinc) for four months at a high risk of bias. Heckmann et al. [262] administered 140 mg (equivalent to 20 mg of elemental zinc) for three months at a low risk of bias. An improvement in taste disorder was observed for the zinc supplement groups (RR 1.61, 95% CI: 1.12–2.31,) among 102 participants *Figure 5.3*.

Stewart-Knox et al. [237] administered zinc gluconate equivalent to 15 or 30 mg of elemental zinc per day over six months and was at high risk of bias. The study showed

that zinc level increased postintervention in both groups and was greater in the 30 mg supplemented group; acuity for salt taste was greater in the 30 mg supplemented group (P=0.031) while 15 and 30 mg Zn groups did not improve any taste acuity. However, we could not conduct a meta-analysis of the results because the study did not report the number of events in the placebo group.

(3) Zinc Picolinate. Of the studies included, only one [353] was found to examine the efficacy of zinc picolinate on taste disorder patients at a high risk of bias. An improvement in taste disorder at a dosage of 28.9 mg three times/d for three months (RR 1.70, 95% CI: 1.13–2.56) *Figure 5.3*, with 73 participants.

(4) Zinc Sulphate. In 1976, Henkin et al. [263], examined the effectiveness of four doses of 100 mg of zinc ion, with an unclear risk of bias. The results from this study indicated that both placebo and treatment groups with zinc sulfate showed equivalent improvements. We excluded this study from the meta-analysis because the number of events in both the intervention and placebo groups was unclear.

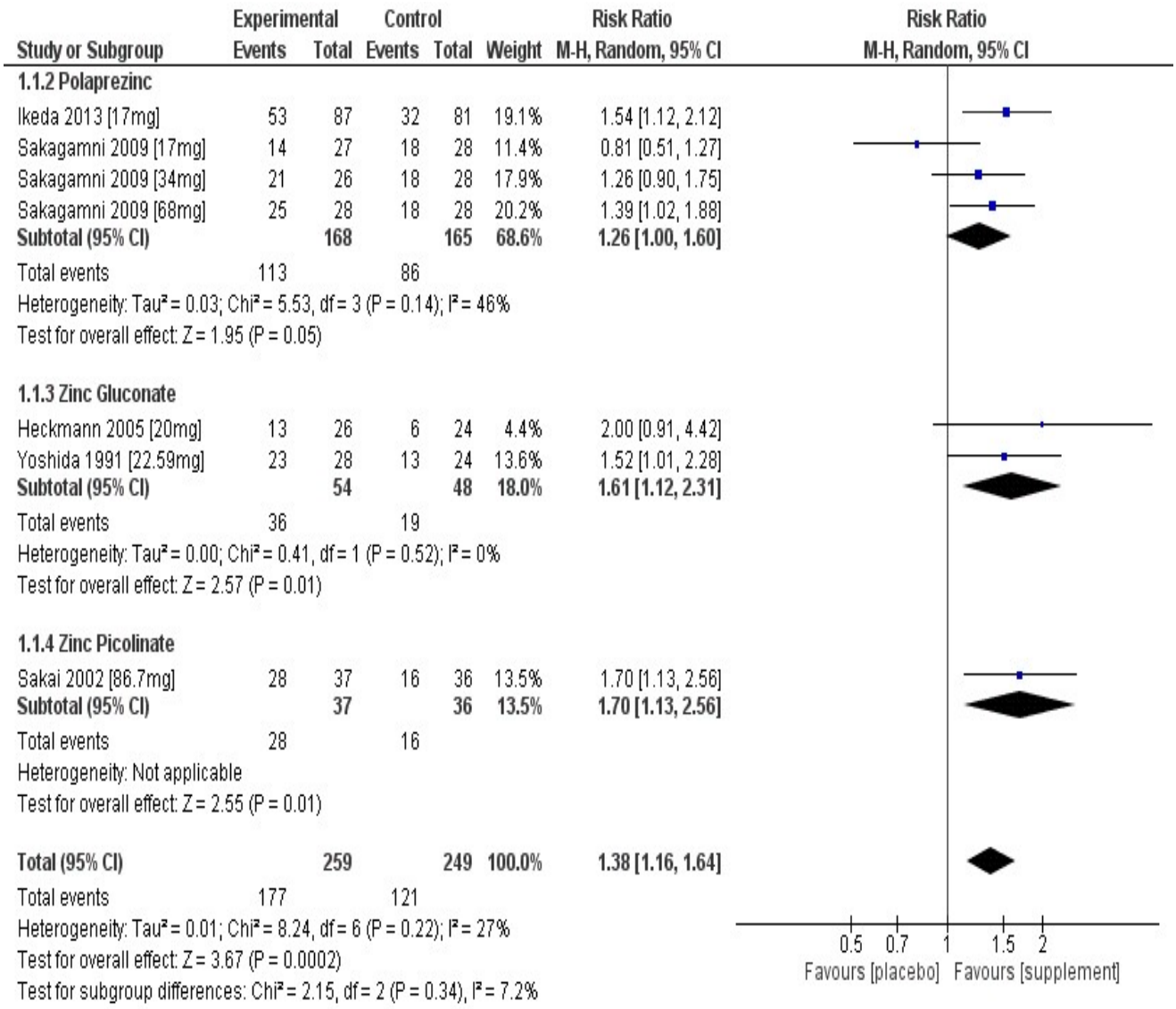


Figure 5.3 Meta-analysis of the effect of zinc replacement for the treatment of taste disorder.

Forest plot including data analysis of five studies with a total of 508 cases of idiopathic and zinc-deficient taste disorder enrolled on experimental (n = 259) and control groups (n = 249). Data expressed as event "total number of cases that improved after receiving the treatment or placebo," and total "total number of participants in either control or experimental group" p-value for heterogeneity was 0.22. The pooled results of this meta-analysis indicated that taste disorder improvement occurred significantly more frequently in the supplemented group compared to the control group. Overall RR is positive (RR = 1.38, 95% CI = 1.16–1.64), and statistical significance was found to be p=0.0002.

5.4.4.2 Zinc disorder secondary to chronic renal failure

Zinc Acetate

Zinc acetate was used as a treatment for taste disorder induced by chronic renal failure in three studies (Mahajan *et al.* 1979, Mahajan *et al.* 1980, Mahajan *et al.* 1982) [346-348]. Each study provided a single data point, with the overall RR for zinc acetate found to be 26.69 (95% CI=5.52-129.06, p<0.0001), *figure 5.4*. The total number of participants in the three studies was 77 patients. A heterogeneity assessment was inconclusive (I^2=0%, p=0.98), *figure 5.4*.

Zinc sulphate

Two studies, Atkin-Thor et al. [261] and Matson et al. [344], examined the efficacy of zinc sulfate in taste disorder induced by chronic renal failure for up to a six-week intervention period. In a double-blind crossover trial, Atkin-Thor et al. [261] introduced 440 mg of zinc sulfate three times per week at a high risk of bias, The results of this study showed a significant improvement in taste acuity in the supplemented group, whereas Matson introduced 220 mg of zinc sulphate per day at an unclear risk of bias, the results from this study showed no improvements in both intervention and placebo groups. These two trials did not provide sufficient details about the placebo groups, so we excluded them from the meta-analysis.

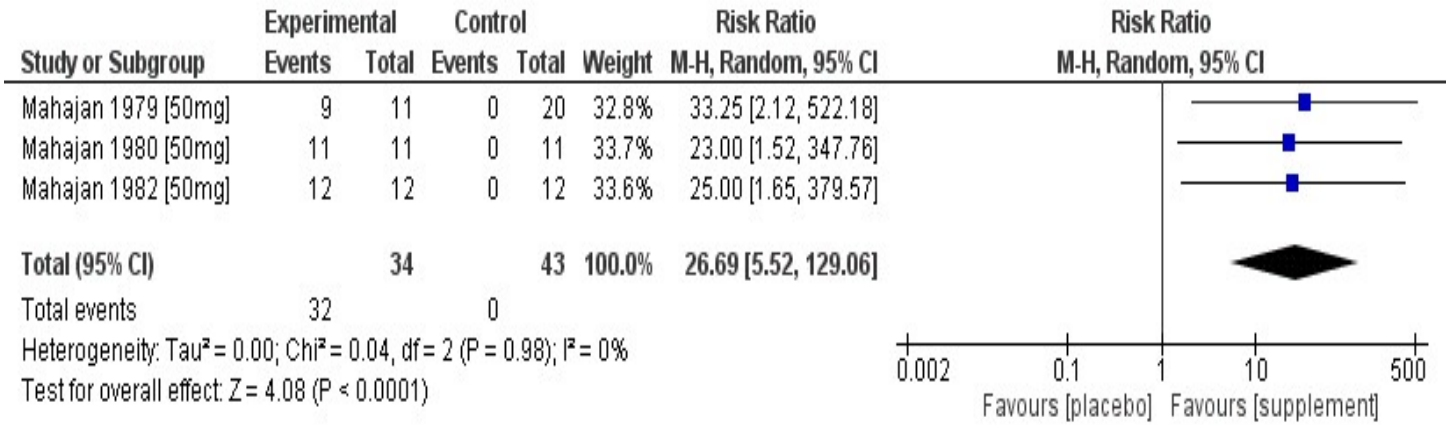


Figure 5.4 Meta-analysis of the effect of zinc replacement for taste disorder in patients with chronic renal failure.

Forest plot including data analysis of three studies with a total of 77 cases of taste disorder induced by chronic renal failure, enrolled to experimental ($n = 34$) and control groups ($n = 43$). Data expressed as event "total number of cases that improved after receiving the treatment or placebo" and total "total number of participants in either control or experimental group" value for heterogeneity was 0.98. The pooled results of this meta-analysis indicated that taste disorder improvement occurred significantly more frequently in the supplemented group compared to the control group. Overall RR is positive (RR = 26.69, 95% CI = 5.52–129.06), and statistical significance was found to be $P<0.0001$.

5.5 Discussion

This systematic review assessed the efficacy of zinc supplementation to improve taste disorders. We focused on outcomes of intervention groups compared to placebo among patients with zinc deficiency and idiopathic taste disorder or taste disorder induced by chronic renal failure. We included 12 randomized controlled trials; four were included in qualitative synthesis and eight in a meta-analysis. We assessed five studies as having an unclear risk of bias [267, 342, 344, 348, 349], four studies at a high risk of bias [256, 260, 261, 345] and three studies at low risk of bias [343, 346, 347]. Seven included studies examined the effectiveness of different zinc supplementations (polapre zinc, picolinate, zinc gluconate and zinc sulphate) among patients with zinc deficiency and idiopathic taste disorder. We did not include two studies - Henkin et al. [349] and Stewart-Knox et al. [260] in the meta-analysis because of their unclear methodologies and unreported data for the placebo groups. Out of seven studies that examined the efficacy of zinc supplementation in taste disorders induced by chronic renal failure, we did not include Atkin-Thor et al. [261] nor Matson et al. [344] in the meta-analysis because they did not report data about the placebo groups.

Summary of main results

The pooled results of this meta-analysis indicated that taste disorder improvement occurred significantly more frequently in the intervention group compared to the control group. There was a significant effect of zinc supplementation at the study level except in three studies [343, 345, 354], there was also a statistically significant effect of zinc supplementation at the meta-analysis level. We found that zinc supplements reduced the risk of taste disorders by 51%. Moreover, the pooled results of the largest studies [256, 267, 342] indicated that zinc supplementation is an effective treatment for taste disorders in patients with zinc deficiency or idiopathic taste disorders when given in high doses ranging from 68–86.7 mg/d for up to three

months. This results in agreement with Yagi et al. [291] review indicated that zinc supplementation contributes to the treatment of taste disorders caused by zinc deficiency. In contrast, Nagraj et al. [355] did not find sufficient trials to support the effectiveness of zinc in taste disorder improvement. The level of included studies ranged from moderate to high using The Grading of Recommendations Assessment, Development and Evaluation (GRADE). Heckmann et al. [343] and Yoshida & Tomita [345] introduced a low dose of elemental zinc, around 20–22.59 mg/d, for up to three to four months to patients with taste disorders induced by zinc-deficiency or idiopathic disease and our meta-analysis showed insignificant improvement of taste disorders, however, the results for these two trials should be viewed with caution due the quality of evidence was rated as low, and high risk of bias for one study Yoshida & Tomita [345].

In the three studies concerning taste disorders induced by chronic renal failure, we found the level of evidence and its quality to be low. This was based on the fact that the studies were mainly small sample sizes and the absence of event numbers of the placebo group; in the meta-analysis, this produced a high upper limit of the CI [346-348]. Overall, per the available data, zinc supplementation appears to confer a greater improvement in taste perception amongst those with chronic renal disease using zinc acetate (overall RR=26.69, 95% CI=5.52-129.06, p<0.0001) *fig 5.4* in comparison to the extent of improvement using alternative supplements in the iatrogenic or zinc deficiency disease groups *fig. 5.3*. Unfortunately, a direct comparison in the response to zinc acetate between chronic renal disease and iatrogenic or zinc deficiency cohorts was not possible due to missing data. Furthermore, zinc picolinate was represented by a single data point [256]. In all studies included in this meta-analysis, I did not find considerable statistical heterogeneity. Nevertheless, there is substantial heterogeneity based on elemental zinc-equivalent dose, supplement chemical structure, follow-up time, and disease state, as

inferred based on the study characteristics as we aimed to collect all available RCTs to examine the effectiveness of zinc supplementation in taste disorder treatment. We suggest that zinc supplementation may improve specific tastes more than others depending on the case or the disease-induced taste disorder. We suggest a high dose of elemental zinc 68–86.7 mg/d for up to six months to improve taste disorders. However, the results of this meta-analysis should be interpreted with caution as excessive zinc supplementation might have serious health outcomes and toxicity if zinc is taken at a significantly higher than the Recommended Dietary Allowance (RDA) (100–300 mg/day vs. 15 mg daily), It has been proposed that even smaller doses of zinc supplementation, closer to the RDA, could interfere with the utilisation of copper and iron and negatively impact HDL cholesterol levels. Zinc supplement users should be informed of any potential risks associated with its usage [86].

Strengths and limitations of this study:

Unlike other reviews in this area, our systematic review provided additional evidence and clarification of zinc supplementation's efficacy in improving taste disorder in adult populations by stratifying according to zinc dose, formulation type and treatment duration. However, One aspect that can limit the analysis and discussion of the results is the heterogeneity of the methods used. The studies assessed combined objective outcomes (e.g. filter paper disk; detection and recognition thresholds for sweet, sour, salty, bitter and umami tastes) and subjective outcomes (e.g. questionnaire results). However, whether the difference between subjective and objective methods could significantly affect the results of improvement is somewhat debatable. In another review, the author examined the overall improvement in taste acuity using both subjective and objective methods; however, the author could not conclude the overall effect because of the very low level of evidence. High-quality research is required to compare different objective and subjective methods [356]. I observed that some studies detected taste improvement in only one type of taste; so, a further limitation of our meta-

analysis is that we defined ‘improvement’ as an improvement of any of the five basic tastes sweet, sour, bitter, salty and umami tastes.

5.6 Conclusion

High-dose zinc supplementation is an effective treatment for taste disorders in patients with zinc deficiency or idiopathic taste disorders and patients with taste disorders induced by chronic renal failure.

Taste change has an important impact on dietary compliance and eating behaviour post-BS. The reporting of dietary compliance however remains subjective, and its accuracy is unclear. In the next chapter, I explored the reporting of calorie intake of patients undergoing very low-calorie diets using two different methods.

Chapter 6: Examining the Compliance with the Recommended Additional Calorie Intake in Middle-aged Overweight Males Who Follow Very Low-calorie Diets (VLCD) (Six Weeks Weight Loss Intervention)

Chapter Overview

Having completed the studies looking at the link between zinc deficiency, taste change and hair loss following BS discussed in previous chapters, VLCD like bariatric surgery relates to significant calorie restriction to induce weight loss and additional metabolic benefits. The previous chapters have highlighted the role of zinc deficiency as a mediator of taste disorder following bariatric surgery. This has a major impact on compliance with eating behaviour and compliance with calorie constriction. Assessment of dietary intake and compliance is a crucial component of dietary monitoring but how reliable are patients reporting their calorie intake? This study included 35 healthy middle-aged male volunteers, who were following VLCD weight loss intervention (meal replacement products provide 600 kcal/ day), participants were also allowed to consume an extra 200 kcal/day in addition to VLCD. The main aim of this study is to investigate the subjects' compliance with the extra calorie intake using two different dietary assessment methods.

6.1 ABSTRACT

Background: Assessment of dietary compliance to calorie restriction (CR) plays an important role in the success of clinical dietary intervention. We examine the compliance to the additional calorie allowance following intake of Very Low-Calorie Diets (VLCDs) meal replacement (equivalent to 600 kcal/day), using two different dietary assessment methods.

Method: 35 healthy middle-aged male volunteers (mean age: 44.3±9.79 years; BMI: 33.3±4.47 kg/m$^{2)}$ were asked to follow a six-week CR programme based on VLCD (600 kcal/day; LighterLife UK Ltd) and allowed the subjects to also consume up to an additional 200 kcal per day from conventional foods or just vegetables and nuts. Daily food intake was monitored using the Nutracheck program (N=12) or manually (N=23).

Results: Participants using Nutracheck recorded total additional calorie intake, median (IQR); 788.2 (193.5) kcal with % macronutrient intake of carbohydrate: 25.7 (6.21); protein: 39.1 (5.61) and fat: 28.93 (3.94). In contrast, subjects who manually recorded their food intake recorded a total additional calorie intake of 161.0 (91.8) kcal. This group reported a high % carbohydrate and low % protein diet, with most of their calorific intake coming from carbohydrates: carbohydrate: 46.7 (21.7), protein: 15.9 (11.7), and fat: 27.9 (21.1). No significant difference in BMI reduction was noted between the two groups. However, there were significant BMI reductions pre and post-intervention in both groups $p < 0.001$.

Conclusion: Patients undertaking CR programme using VLCD with an additional food allowance from conventional food on top or food intake restricted in vegetables and nuts, often exceed the total calories allowed per day. The reporting of compliance significantly varies according to how they are monitored.

6.2 Introduction:

Interest has emerged in recent years regarding the role of hypoenergetic Very Low-Calorie Diets (VLCD) in the management of excess weight and obesity in patients with and without Type 2 diabetes [357, 358]. In supervised situations, a VLCD consists of meal replacement products that form a complete nutritional profile of vitamins and minerals with a balanced macronutrient profile and has been associated with significant health benefits [22, 23]. This is administered in the form of <800 Kcal/d (3347KJ/d) diet with the macronutrient composition calculated to maximise weight loss while minimising lean body mass loss, with compliance generally being reported to be good [359, 360]. While VLCDs are generally safe, the weight loss induced by such hypoenergetic diets can lead to between 20 to 30% loss of lean body mass (LBM)[361, 362]. Exercise and increased protein intake have been employed by researchers to reduce any loss of lean body mass during VLCD [22], with variable success [363]. Assessment of dietary intake and compliance is therefore important. This is particularly relevant in calorie restriction (CR) plans which provide patients with the capacity to consume an additional 200 Kcal/day evening meal from any food source [364]. Within this CR plan, the determination of any remaining calorie consumption with the aim to enhance compliance and palatability, is often entrusted to the discretion of the individual partaking in the dietary regimen. There are no previous studies which examined compliance with this extra calorie intake. We therefore assessed the reporting of these additional intakes using two different dietary assessment methods based on dietary records.

Aim and Rational

Modern Very Low-Calorie Diets (VLCDs) aim to consume no more than 2510 kJ (or 600 kcal) per day, mostly via the use of readily available commercial meal replacements. The determination of any remaining calorie consumption is often entrusted to the discretion of the individual partaking in the dietary regimen. There are no previous studies that examined compliance with this extra calorie intake. Therefore, for this experimental study and to further improve compliance, our calorie restriction strategy allows the consumption of an additional 200 Kcal evening meal on top of a 600 Kcal plan. In this study, we assessed the reporting of these additional intakes using two different dietary assessment methods based on dietary records. These 3 groups were in this study to find out the outcomes difference between the different methods used in food records and to examine the difference between the compliance when subjects had no food restriction and when restricted food intake in vegetables and nuts.

6.3 Materials and Method

Study Design

This research was carried out at the Graduate Entry Medical School, based at the Royal Derby hospital as part of a physiological study to investigate the effects of VLCD on muscle metabolism. The design of this study was part of a larger, departmental study. The study protocol was approved by the East Midlands – Derby Research Ethics Committee of the NHS health research authority, IRAS project ID:255016, *see appendix 7*. Voluntary informed consent was obtained from each subject before entry to the study.

The inclusion criteria were overweight/obese patients (BMI≥27) who were middle-aged (30 to 62-year-old) males. All participants underwent a thorough medical examination, including a medical history assessment, blood tests and an ECG. Subjects with uncontrolled hypertension (BP>180/110), significant or recent cardiovascular or respiratory history, epilepsy, irritable bowel disease or active renal illness, cancer, clotting problems, musculoskeletal or neurological issues, known sensitivities or allergies to contrast dyes, diabetes or family history of early death (<55 years old) from cardiovascular disease were excluded.

Eligible subjects who agreed to participate in the study were then randomly assigned to one of three groups: group 1: Digital program users, record their food intake using the Nutracheck program and they had no food restriction n=12; group 2: manual food records also had no food restriction; n=9 (Nutritics software were used for energy and macronutrients analysis [365]) ; group 3: manual food records and food intake restricted in vegetables and nuts n=14. All subjects were trained to use the App (details of the food composition database illustrated in *appendix 8*) and for the manual food record and they recorded the additional food intake by themselves. All were given recommendations about the protein content of the additional foods they were permitted. Participants in group 3 were given a sheet contain information about amount and examples of allowed nuts and vegetables, *see appendix* 9. All subjects were then subjected to a six-week VLCD nutritional intervention using LighterLife VLCD Foodpacks. These were equivalent to 600 Kcal per day, as well as providing 100 per cent of the RNI of all major vitamins and minerals. LighterLife creates meal replacements that are consumed as four food packs each day, which may take the form of soups, shakes, textured meals and bars. The subjects were asked to restrain any extra food intake within 200 Kcal/d and were provided dietary advice. To ensure patient compliance, they were contacted by telephone two or three times each week, to remind them about the diet and to allow them to discuss any issues they were encountering. Nutritional intake (VLCD plus any additional food intake) was recorded

in a diet diary for each participant. The 3 groups in this study were to find out the outcomes difference between the different methods used in food records and to examine the difference between the compliance when subjects had no food restriction and when restricted food intake in vegetables and nuts.

Evaluations:

Prior to the commencement of the VLCD course, patients' age, gender, body weight (BW), and BMI were recorded, to calculate the amount and percentage of total weight loss (per cent TWL) created by the VLCD. Total weight loss and patient compliance with limitations on additional food consumed were assessed after the course, with the latter measured by calculating the calorie content of the additional food consumed and reported. The percentage of calorie content provided by the various macronutrients consumed was also calculated.

Statistical analysis:

The VLCD participants were divided into Nutracheck users and self-reporting individuals, and their outcomes were compared statistically. This comparison included calculating participants' energy consumption (Kcal), along with their relative intakes of fat (%), protein (%), and carbohydrates (%). A Student's t-test was used to compare the differences in means between groups for normally distributed variables, while the Wilcoxon rank-sum test was used to compare differences in medians between groups with heavily skewed distributions. The statistical significance was set at a p-level of 0.05, with all analyses completed and illustrated in Stata/SE Statistical Software version 16.1 (StataCorp., College Station, TX).

6.4 Results

6.4.1 Demographic data at baseline:

Thirty-five male participants were recruited in this study. The mean age was 44.3±9.79 years (range 30 to 62), and the mean body weight and BMI in pre-VLCD were 106.0±17.2 kg (range 79 to 148) and 33.3±4.47 kg/m^2 (26.7 to 44.2), respectively. More details on the baseline characteristics for the different intervention groups are shown in *table 6.1*.

Table 6.1 Participant baseline Characteristics for NutraCheck users, manual not restricted and manual restricted groups.

Demographic data	Digital program user (Nutracheck)	Manual food record (Not restricted)	Manual food record (food-restricted in vegetables and nuts)
Total Participants, n (%)	12 (34.3)	9 (25.7)	14 (40.0)
Age in years, mean (SD)	44.7 (8.88)	41.3 (8.63)	46.2 (11.3)
BW kg pre-VLCD, mean (SD)	99.8 (13.3)	100.9 (10.5)	114.9 (20.4)
BMI kg/m^2 pre-VLCD, mean (SD)	32.2 (3.71)	32.2 (2.84)	35.0 (5.53)

6.4.2 A comparison between digital program users (Nutracheck) and manual records:

Participants in this study recorded their dietary intake with respect to the permitted 200 Kcal supplement using two different dietary assessment methods. The first group used a digital program (Nutracheck, n = 12), while the second group recorded the food manually (n = 23). Of those using manual food intake records, 9 were not restricted to specific kinds of food, whereas 14 participants of manual users were restricted to vegetables and nuts. The 23 participants were involved in recording their dietary intakes manually across six sheets.

6.4.2.1 % Macronutrient and calorie intake differences between groups.

These results show that participants who used a digital program to record their dietary intake consumed more calories (Median (IQR) = 788.21 (193.6)) than participants who recorded their food manually 161.0 (91.8) ; $p < 0.001$). The results also indicated that digital program users' calorie intake from protein was highest, at 39.1 (5.61) %, followed by fat at 28.93 (3.94) %, and then carbohydrates at 25.7 (6.21) %. In contrast, the highest calorie intake for the participants who recorded their food manually came from carbohydrates 46.7 (21.7) %, then fat 27.9 (21.1) %, and then protein 15.9 (11.7) %. There were thus significant differences between the groups in terms of calorie intakes from protein and carbohydrates $p < 0.001$ (Table 6.2). There were no statistically significant differences between the manual food records groups in terms of calorie intakes and calories from protein, fat and carbohydrates $p < 0.001$. (Table 6. 3).

In a subanalysis, we also compared digital program (nutracheck) user with participants who recorded their food manually where both groups had the additional calorie non-restricted to macronutrient type. The findings for this sub group were similar to the full results which showed that participants who used digital program to record their dietary intake, consumed more calories; Median (IQR) (788.21(193.58)) than participants who records their food manually 188.02(148.25); P=0.0001. The results also indicated that the most calories intake for the digital program user came from protein 39.095 (5.615) %, fat 28.935(3.94)%, and then carbohydrate 25.715(6.215)%. While the most calorie intake for the participants who records their food manually came from carbohydrate 51.15 (16.87) % , fat 24.4(6.88)% and then protein 22.76(9.37) respectively. There were a significant difference between groups in term of calories intake from proteins p=0.001and carbohydrates p=0.0001. *See table 6.4.*

Table 6.2 Calorie and macronutrient consumption outcomes by dietary recording method:

Dietary recording method	Digital program user (Nutracheck): n= 12	Manual food record = 23	Probability of a difference
	Median (IQR)	Median (IQR)	
Calories/kcal	788.2 (193.5)	161.0 (91.8)	$Z_{(35)} = -4.79$; $p < 0.001$
Protein%	39.1 (5.61)	15.9 (11.7)	$Z_{(35)} = -4.24$; $p < 0.001$
Fat%	28.93 (3.94)	27.9 (21.1)	$Z_{(35)} = 0.07$; $p = 0.95$
Carbohydrate%	25.7 (6.21)	46.7 (21.7)	$Z_{(35)} = 3.30$; $p < 0.001$

Table 6.3 Calorie and macronutrient consumption outcomes by manual food records:

Dietary recording method	Manual food record (no food restriction): N = 9	manual food record (food restricted in vegetables and nuts) = 14	Probability of a difference
	Median (IQR)	Median (IQR)	
Calories/kcal	188.0 (148.3)	148.8 (104.2)	$Z_{(23)} = 1.51$; $p = 0.14$
Protein%	22.8 (9.37)	14.3 (7.01)	$Z_{(23)} = 2.33$; $p = 0.019$
Fat%	24.4 (6.88)	34.9 (24.7)	$Z_{(23)} = -1.70$; $p = 0.09$
Carbohydrate%	51.15 (16.9)	42.2 (27.1)	$Z_{(23)} = 1.89$; $p = 0.058$

Table 6.4 Calories and macronutrients consumptions outcomes regarding the dietary recording method (nutracheck vs manual food record "not restricted")

Dietary recording method	Digital program user (nutracheck): n= 12	Manual food record = 9	Probability of a difference
	Median (IQR)	Median (IQR)	
Calories/kcal	788.21(193.58)	188.02(148.25)	z = -3.838; P=0.0001
Protein%	39.095 (5.615)	22.76(9.37)	z = -3.26; p=0.001
Fat%	28.935(3.94)	24.4(6.88)	z = -1.77; p=0.075
Carbohydrate%	25.715(6.215)	51.15 (16.87)	z = 3.838; p=0.0001

6.4.3 Weight loss

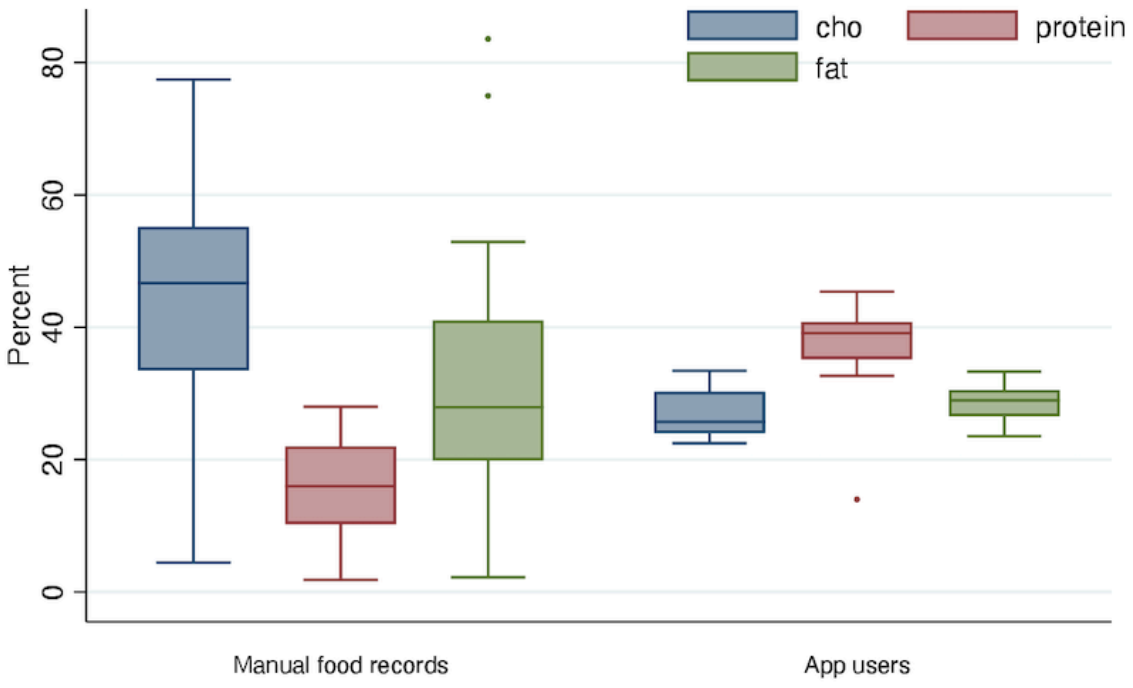
These results show that the manual food record group lost more weight on average than the digital program users. Similar BMI reduction was noted among the manual food records and the digital program uses mean difference of 3.42 and 3.25 respectively. However, there was a

statistical significance in BMI reduction pre and post-intervention among the two groups $p <$ 0.001 (Table 6.5).

Table 6.5 Change in BMI (kg/m^2) of manual recorders versus digital program (Nutracheck) users.

Dietary recording method	**Manual food record: n = 23**	**Digital program user (Nutracheck): n = 12**
BMI pre, mean (SD)	33.9 (4.79)	32.2 (3.71)
BMI post, mean (SD)	30.5 (5.08)	28.9 (3.44)
Mean difference, (95%CI)	3.42 (2.96 – 3.87)	3.25 (2.62 – 3.88)
Test of a difference	$t_{23} = 15.5$, $p < 0.001$	$t_{12} = 11.4$, $p < 0.001$

Figure 6.1 Micronutrient intake by dietary recording methods.



6.5 Discussion

Assessment of dietary intake as part of the CR programme is crucial in managing and monitoring treatment compliance. Our study showed significant differences in patients' reporting of additional food intake according to how food consumption is recorded. Our study showed that digital program users reported significantly higher calorie consumption than allowed - significantly exceeding triple the recommended 200 Kcal intakes for a median value of 788.21 kcal - compared with participants who reported them manually. No significant difference was noted in the weight loss.

Most participants ate generous amounts of solid food such as chicken, meat, and rice. The number of calories consumed varied across study days, though, overall, the results indicated that these participants were unable to adhere to the additional CR. This result may be interpreted in several ways. The first is that using a digital program to keep food records helped participants to choose high protein and low carbohydrate foods, as the program reported macronutrient content for each food item. This way of recording dietary intake helped participants to receive direct feedback about their diet. Previous research has investigated the impact of daily feedback messages on dietary adjustments among obese people, revealing positive outcomes, as using mobile devices may significantly contribute to the decrease in calorie and fat consumption[301]. However, the participants who used this technology may thus less focused on the total calories content of all the extra food consumed each day. The second interpretation is that eating similar food products every day may lead to a loss of food enjoyment, causing participants to tend to eat more calories (when allowed) in their extra meals to experience more enjoyment as the study period progressed. Third, despite the VLCD featuring a high fibre and low carbohydrate composition, participants still felt hungry during

the day, eating more to redress this. However, given that there were no significant differences in weight loss between the two groups, it is likely that rather than better compliance, the manual recording group may have underestimated their reporting of the additional allowable calorie intake. Nonetheless and importantly, despite participants' reported extra calorie intakes, participants still lost a significant proportion of weight during the study period, with an average of around 10.14kg each lost during the six weeks for an average of 1.69 kg/week. The observed weight losses from our CR study are comparable to what was reported in previous studies using VLCDs [366, 367].

Participants who recorded their food intake manually, reported additional calorie consumption within the allowable 200 Kcal limit, at the expense of consuming a high carbohydrate and low protein diet. This macronutrient effect may be due to two reasons: poor nutritional knowledge concerning high protein content foods and the ongoing absence of dietitian monitoring. We found that the use of application is more accurate than manual food records offered versatile dietary and exact food portion size that made it applicable in both clinical and research environments. As digital program users choose to eat more sources of protein, this result potentially offers an insight into the advantages of using programmatic help and guidance for participants who are required to consume high-protein food sources. Nonetheless, since participants may not record the correct quantity and portion sizes of consumed food during the manual recording of food intake, it is conceivable that reporting manually may underestimate the total calorie intake. Furthermore, writing down the food consumed at the end of a day manually is more likely to be less accurate than recording food as it is consumed. The confounding factor of this study was that the participants were enrolled into different training activities level groups which may affect the eating behaviour of participants in different study groups. In addition, another limitation of this study that all participants were of male gender.

6.6 Conclusion

The study has multiple limitations including small number of participants, participants were not contacted daily to ensure compliance with the methods of monitoring food intake, and data for individuals on manual food monitoring included was combined for those who's 200 Kcall additional diet was restricted and not restricted. For the later, we also undertook subanalysis where we compared data food those who additional allowable calorie intake was not restricted to types of food and macronutrient. Nonetheless, we observed that participants receiving a CR diet may exceed the total calories allowed per day by consuming extra calories from additional calorific sources. Using an app to track food intake may help participants comply with high protein and low carbohydrate requirements, yet it appears to encourage participants to consume more calories overall. Participants keeping manual food records report calorie intake within allowable limits, although, this may be due to underreporting. Assessment of dietary compliance to the additional calorie intake should therefore take into account how participants record their intake.

Chapter 7: General Discussion and Conclusion

Chapter Overview

The objective of this chapter is to conduct a comprehensive evaluation and synthesis of the primary outcomes presented in the preceding chapters. The primary outcome of each chapter is examined in relation to the wider body of existing scholarly works. Additionally, this chapter addresses the limitations of the study and provides recommendations for future research. The concluding remarks include the objectives and goals of the thesis by succinctly outlining the significance of the findings, so offering guidance for enhancing future research endeavours aimed at gaining a more comprehensive understanding of the relation between zinc deficiency and taste change following BS.

7.1 Discussion

The thesis focused on examining two main objectives; the first object is to explore the potential links between lower zinc levels and complications after bariatric surgery such as; taste change, salivary flow rates and hair loss. The second objective is to investigate the patient's ability to comply with the additional calorie intake in participants who follow VLCD for up to 6 weeks. This investigation will develop an insight into the long-term effectiveness of VLCD in weight reduction and adequate zinc supplementation after bariatric surgery**.**

Chapter 2

The data of systematic review in chapter two illustrated that there were numerous studies carried out on the taste change following BS, however, none of them explored the role of zinc deficiency in reported taste change following BS. The results were different depending on the methods used to assess taste change support. For example, several survey studies have reported that a significant proportion of patients have reported experiencing alterations in taste perception after undergoing bariatric surgery. These taste changes often occur about six months after the surgical procedure, as indicated by several sources [136, 137, 139, 172]. This finding is in line with a comprehensive study conducted by Ahmed and Penney [176]. Nevertheless, research investigations that used experimental techniques such as recognition thresholds, functional magnetic resonance imaging (fMRI), and the sweetness acceptability test did not yield substantial evidence of taste alteration after BS [138, 171]**.** The previous literature about zinc deficiency and taste disorder only investigated certain cases such as chronic renal failure, disorders in patients with zinc deficiency, and idiopathic taste disorders or cancer patients.

Chapter 4a

The findings of chapter four support the main hypothesis in this thesis that zinc deficiency may induce taste change following bariatric surgery. In disagreement with the previous literature,

the results of the survey and taste strip examination all showed a significant proportion of patients experience taste change. For example, survey results were subsequently validated through the administration of taste strip tests. The findings derived from the questionnaire indicate that the incidence of taste change among patients who underwent sleeve gastrectomy (SG) was observed to be greater at the 6-month, with a prevalence rate of 45%, compared to the 36% prevalence rate observed at the 3-month post-surgery. Conversely, in the case of patients who underwent gastric bypass (GB) surgery, the prevalence rate was notably high at 3 months post-surgery, reaching 72%, but subsequently decreased to 52% at the 6-month. A comparative analysis conducted using taste strips during the 3-month and 6-month postoperative periods revealed a greater prevalence of hypogeusia among patients who underwent gastric bypass (GB) surgery in contrast to those who underwent sleeve gastrectomy (SG) surgery. The findings of this study suggest that hypogeusia is a common adverse effect following both forms of bariatric surgery, with a higher prevalence observed among individuals who underwent gastric bypass. During the follow-up period, a majority of patients who had undergone bariatric surgery (BS) had reduced salivary flow rates, with over 50% experiencing low to very low levels. This is the first study to examine the potential link between zinc levels and taste change after bariatric surgery. Future research could investigate the effectiveness of different zinc doses of zinc supplementation in taste change treatment following BS through randomized controlled trials. In addition, investigate whether the dose of zinc replacement needed for short period of time and then require a maintenance dose rather than providing constantly high dose of zinc.

Chapter 4b

The studies into the link between zinc deficiency and hair loss following BS is very rare. In addition, there are no previous studies comparing sleeve gastrectomy and gastric bypass in terms of hair loss and zinc deficiency. The results of the study in chapter 4b provided an

interesting result about zinc deficiency and hair loss following BS and a comparison between SG and GB. The data indicated that the prevalence of hair loss among patients who underwent gastric bypass surgery (GB) was twice as high as that among patients who underwent sleeve gastrectomy (SG), with rates of 66.6% and 32% respectively, three months post-surgery. These results demonstrate a statistically significant difference between the two groups. The results of this chapter in agreement with the previous study which examined the effect of zinc deficiency on hair loss among females who underwent SG and indicated that patients suffering from hair loss had low levels of zinc in their blood. Deeper knowledge of the other factors affecting hair loss following BS is needed. Future studies could use a validated hair loss examination for more precise results.

Chapter 5

The study in chapter four only examined the association between taste change and zinc deficiency without introducing any additional zinc supplementation except the routine multivitamins supplementation that the surgeon prescribed after the procedures. To our knowledge, there were no previous studies examining the effectiveness of zinc deficiency in taste change following BS. However, previous literature about zinc deficiency and taste disorder only investigated certain cases such as chronic renal failure, disorders in patients with zinc deficiency, and idiopathic taste disorders or cancer patients.

The results of the systematic review and meta-analysis in chapter five indicated that zinc supplementation is a successful intervention for taste abnormalities in individuals who have zinc insufficiency, idiopathic taste disorders, and taste disorders caused by chronic renal failure. This treatment has shown efficacy when administered in high levels, typically ranging from 68 to 86.7 mg/d, for a duration of up to six months. The findings of this chapter can be an indication for future research to investigate the effectiveness of zinc supplementation in taste change treatment among bariatric patients.

Chapter 6

Patients who are following VLCD and are provided with an additional food allowance from traditional sources or have their food consumption confined to vegetables and nuts, frequently exceed the prescribed daily calorie limit. The manner in which compliance is reported exhibits considerable variation depending on the method of monitoring employed. The results from this chapter suggested that VLCD is an effective short-term solution for weight reduction, however, by monitoring food intake from the additional 200kcal allowance, the results showed that subjects used App to record the additional food intake exceeded the daily calorie allowance by nearly triple the amount. This means that, despite the effectiveness of VLCD in short-term weight reduction, people with obesity may find difficulties in adhering to the VLCD in the long term. Methods used to monitor dietary intake may also impact on the accuracy of reported food intake. This needs to be factored in when assessing compliance to dietary restriction. More studies in this area are needed to examine the long-term compliance to VLCD and the optimal methods of monitoring dietary compliance.

The other important findings of this thesis

In this study, throughout an interview, we also note that all patients who underwent GB underwent SG several years before GB, 39% of GB patients underwent this surgery due to weight regain or weight stability and 86% of them have childhood obesity.

Patients in this research also asked whether they were happy with bariatric procedures as an effective way for weight reduction; all patients who underwent SG answered yes. However, 56% of GB patients answered NO due to the complications they experienced after the surgery.

7.2 The novel findings of this project are summarized as follows:

1. Hypogeusia is more common after GB compared to SG.
2. People at 6 months after GB have lower zinc levels compared to those after SG, which may suggest a link between low zinc levels and hypogeusia after GB.
3. Between people reporting severe hair loss at 6 months after BS, the prevalence of zinc deficiency is high.
4. BS results in low to very low salivary flow rates.
5. Patients enrolled in CR programmes with VLCD and supplementing their diet with traditional foods or restricting their consumption of nuts and vegetables often consume more calories than their daily allotment. The way that compliance is monitored has a major impact on how it is reported.

7.3 Suggestions for future studies:

1. Effectiveness of high doses of zinc supplementation in taste disorder treatment among bariatric surgery patients.
2. The effectiveness of zinc supplementation in improving salivary flow rate among bariatric surgery patients.

7.4 Limitations

BS is noted to cause some side effects and complications frequently become apparent several years after the treatment and include a variety of gastrointestinal problems as well as the requirement for additional endoscopic or surgical interventions, for instance, due to the presence of an internal hernia, GERD and marginal ulcers or due to weight regain. Commonly sleeve gastrectomy is used as a single-stage bariatric procedure. After several years, some patients are required to undergo another type of bariatric surgery such as gastric bypass to treat

the above-mentioned complications such as GERD and weight regain. So one of the limitations of our study is that all GB patients underwent SG before at least 4 years of GB.

The potential confounding in the study in chapters four is that due to the extreme circumstances of COVID-19, the data collected related to GB later than the SG. In addition, some suffered from COVID symptoms which include loss of taste at least two weeks before the visit, which may affect the outcomes.

7.5 Conclusion

The findings of this study can be understood as, using a survey and taste strips, it has been determined that following GB are more likely than SG to experience a change in taste, particularly six months after surgery. These alterations paralleled the lower zinc concentrations at 6 months following GB compared to SG. During the follow-up, more than half of all patients who had undergone BS had low to very low salivary flow rates. This may indicate a link between lower zinc levels and decreased salivation in patients with hypogeusia after BS. Hair loss is a commonly seen adverse outcome after both types of bariatric surgery procedures. However, individuals who undergo GB surgery tend to experience a higher incidence of hair loss, with a significant difference between the two groups and was linked to reduced zinc levels. VLCD is another successful short-term treatment for obesity. However, patients who are following a very low-calorie diet (VLCD) and are given an additional food allowance from traditional sources or have their food intake confined to vegetables and nuts, frequently consume more calories than the prescribed daily limit. How compliance is reported exhibits substantial variation based on the methods employed for monitoring.

Future investigations are necessary to validate the kinds of conclusions that can be drawn from this study. Future research should consider the potential effects of zinc supplements in taste change treatment following BS. It might extend the explanations of low salivary flow rate and taste alteration among bariatric patients.

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APPENDICES

Appendix 1: Search strategies for the systematic review (Chapter 2).

PubMed

Searches	Results
("Zinc"[Mesh] OR "Zinc Sulfate"[Mesh]) AND "Taste Disorders"[Mesh]	162
"Taste Disorders"[Mesh] AND "Bariatric Surgery"[Mesh]	7
("Zinc Sulfate"[Mesh] OR "Zinc"[Mesh]) AND "Bariatric Surgery"[Majr]:	47
((("Bariatric Surgery"[Mesh]) AND "Taste Disorders"[Mesh])) AND ("Zinc"[Mesh] OR "Zinc Sulfate"[Mesh]):	1

Embase:

Search history sorted by search number ascending

AMED

Search history sorted by search number ascending

Searches	Results	Type
1 Weight loss/ and Surgery/	20	Advanced
2 Taste disorders/	13	Advanced
3 Zinc/	132	Advanced
4 1 and 2	0	Advanced
5 1 and 2 and 3	0	Advanced
6 2 and 3	1	Advanced
7 1 and 3	0	Advanced

MEDLINE.

Search history sorted by search number ascending.

Searches	Results	Type
1 Bariatric Surgery/	9505	Advanced
2 Taste Disorders/	1585	Advanced
3 Zinc/ or Zinc Sulfate/	59943	Advanced
4 1 and 2	1	Advanced
5 1 and 3	15	Advanced
6 1 and 2 and 3	0	Advanced
7 2 and 3	137	Advanced

Appendix 2: PICO for the systematic review (Chapter 2)

The PICO tool was used to define the review question.

P	Patient and Problem	All participants are patients underwent bariatric surgery or patients with taste disorder.
I	Intervention	Zinc supplementations
C	Comparison or Intervention	Participants not received zinc supplementation
O	Outcome you would like to measure or achieve	Zinc level, taste thresholds improvement
	Question you are asking	What is the role of zinc deficiency in taste change in patients with or without bariatric surgery ?
	Type(s) of studies you want to find	Randomized controlled trial and cohort studies.

Appendix 3: Quality assessment

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort

a) Truly representative ***(one star)***

b) Somewhat representative ***(one star)***

c) Selected group

d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort ***(one star)***

b) Drawn from a different source

c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g., surgical record) ***(one star)***

b) Structured interview ***(one star)***

c) Written self-report

d) No description

e) Other

4) Demonstration that the outcome of interest was not present at start of study

a) Yes ***(one star)***

b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders

a) The study controls for age, sex and marital status ***(one star)***

b) Study controls for other factors (list) _____ ***(one star)***

c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome

a) Independent blind assessment ***(one star)***

b) Record linkage ***(one star)***

c) Self report

d) No description

e) Other

2) Was follow-up long enough for outcomes to occur

a) Yes ***(one star)***

b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above:_____

3) Adequacy of follow-up of cohorts

a) Complete follow up- all subject accounted for ***(one star)***

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. ***(one star)***

c) Follow up rate less than 80% and no description of those lost

d) No statement

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE: RANDOMIZED CONTROLLED TRIAL

Note: A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Exposure
categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

a) yes, with independent validation *

b) yes, e.g., record linkage or based on self-reports

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases *

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls *

b) hospital controls

c) no description

4) Definition of Controls

a) no history of disease (endpoint) *

b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for _____ (Select the most important factor.) *

b) study controls for any additional factor * (This criteria could be modified to indicate specific
control for a second important factor.)

Exposure

1) Ascertainment of exposure

a) secure record (e.g. surgical records) *

b) structured interview where blind to case/control status *

c) interview not blinded to case/control status

d) written self-report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes *

b) no

3) Non-Response rate

a) same rate for both groups *

b) non respondents described

c) rate different and no designation

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 4. Questionnaires and informed consent

استبيان قياس تغيير حاسة التذوق والشهية بعد عمليات انقاص الوزن

Questionnaire to measure taste change and appetite following bariatric surgery

Patient Name:	**اسم المريض/ة:**
Age	**العمر:**
Gender: *Male *Female	**الجنس: *ذكر * أنثى**
Weight	**الوزن:**
Height:	**الطول:**
BMI:	**معدل كتلة الجسم:**
EWL%	**نسبة خسارة الوزن:**
Type of Surgery: *LSG *RYGB	**نوع العملي: *تكميم *تحويل مسار كامل**
Zinc Level	**مستوى الزنك في الجسم:**
Date: ……/……./……	**التاريخ: ……/……/……**

ملاحظة: جميع المعلومات في هذا الاستبيان سرية ولا تستخدم الا لأغراض البحث العلمي.

Note: All information in this questionnaire is confidential and is used only for scientific research purposes.

Please circle the most appropriate answer or circle the relevant number on the scale (1–10)					يرجى وضع دائرة حول الإجابة الأكثر ملاءمة أو وضع دائرة حول الرقم ذي الصلة على المقياس (1-10)			
Q1.	Have you noticed any change in your appetite since your weight loss surgery?	Yes	No		لا	نعم	هل لاحظت أي تغيير في شهيتك منذ جراحة إنقاص الوزن؟	س1
Q2.	Have you noticed any change in the taste of food or drink since your weight loss surgery?	Yes	No		لا	نعم	هل لاحظت أي تغيير في مذاق الطعام أو الشراب منذ جراحة إنقاص الوزن؟	س 2
Q3	Have you noticed any change in your sense of smell since your weight loss surgery?	Yes	No		لا	نعم	هل لاحظت أي تغير في حاسة الشم لديك منذ جراحة إنقاص الوزن؟	س 3
Q4	Have you experienced an overall loss of taste since your weight loss surgery?	Yes	No		لا	نعم	هل تعرضت لفقدان حاسة التذوق بشكل عام منذ جراحة إنقاص الوزن؟	س4

***إذا أجبت بـ "نعم" على الأسئلة أعلاه ، فيرجى المتابعة إذا أجبت بـ "لا" على جميع الأسئلة أعلاه ، فلا تتابع أكثر من ذلك , شكرا و يرجى إعادة الاستبيان.**

***If you answered YES to the above questions, please continue. If you answered NO to all of the above questions, do not proceed any further. Thank you and Please return the questionnaire.**

Q5	If you have had a loss of taste, is that loss:	Complete	Partial	No loss				إذا كنت قد فقدت حاسة التذوق ، فهل هذه الخسارة:	س5
Out of 10	1 2 3 4 5 6	7 8	9	10	10	9	8	7 6 5 4 3 2 1	من 10:
Q6	Are there any foods that are repulsive or intolerable to you since your weight loss surgery?		Yes	No	لا	نعم		هل هناك أي أطعمة مثيرة للاشمئزاز أو لا تطاق بالنسبة لك منذ جراحة إنقاص الوزن؟	س6
If you answered YES, then please state what:					إذا أجبت بنعم يرجى ذكرها:				
Q7	Are there any foods that taste different to you since your weight loss surgery?		Yes	No	لا	نعم		هل هناك أي أطعمة تشعر باختلاف مذاقها عن المعتاد منذ جراحة إنقاص الوزن؟	س7
If you answered YES, then please state what:					إذا أجبت بنعم يرجى ذكرها:				
Q8	Has your overall taste increased in intensity since your weight loss surgery?		Yes	No	لا	نعم		هل ازدادت حدة ذوقك العام منذ جراحة إنقاص الوزن؟	س8
Q9	Have you experienced an increase in taste for sweet foods?		Yes	No	لا	نعم		هل واجهت زيادة في مذاق الأطعمة الحلوة؟	س9
Q10	Have you experienced a decrease in taste for sweet foods?		Yes	No	لا	نعم		هل عانيت من انخفاض في مذاق الأطعمة الحلوة؟	س10

Q11	If you have had a loss of sweet taste, is that loss:							Complete		Partial	No loss	لا خسارة	جزئية	كاملة	إذا كنت قد فقدت الطعم الحلو ، فهل هذه الخسارة:	س11
Out of 10	1	2	3	4	5	6	7	8	9	10	10	9	8	7	6	5	4	3	2	1	من 10	كم
Q12	Have you experienced an increase in taste for salty foods?									Yes	No	لا	نعم	هل عانيت من زيادة في مذاق الأطعمة المالحة؟								س12
Q13	Have you experienced a decrease in taste for salty foods?									Yes	No	لا	نعم	هل عانيت من انخفاض في مذاق الأطعمة المالحة؟								س13
Q14	If you have had a loss of salty taste, is that loss:							Complete		Partial	No Loss	لا خسارة	جزئية	كاملة	إذا كنت قد فقدت الطعم المالح ، فهل هذه الخسارة:								س14
Out of 10	1	2	3	4	5	6	7	8	9	10	10	9	8	7	6	5	4	3	2	1	من 10	كم
Q15	Have you experienced an increase in taste for sour foods?									Yes	No	لا	نعم	هل عانيت من زيادة في مذاق الأطعمة الحامضة؟								س15
Q16	Have you experienced a decrease in taste for sour foods?									Yes	No	لا	نعم	هل عانيت من انخفاض في مذاق الأطعمة الحامضة؟								س16
Q17	If you have had a loss of sour taste, is that loss:							Complete		Partial	No Loss	لا خسارة	جزئية	كاملة	إذا كنت قد فقدت حاسة التذوق ، فهل هذه الخسارة:								س17
Out of 10	1	2	3	4	5	6	7	8	9	10	10	9	8	7	6	5	4	3	2	1	من 10	كم
Q18	Has this change in taste affected how much you eat?									Yes	No	لا	نعم	هل أثر هذا التغيير في المذاق على مقدار ما تأكله؟								س18
Q19	In your opinion, has your change in taste affected your weight loss?									Yes	No	لا	نعم	برأيك ، هل أثر التغيير في المذاق على فقدان الوزن؟								س19
Q20	Overall, do you feel that your taste has increased or decreased in intensity since your weight loss surgery?									Increased	Decreased	انخفض	زاد	بشكل عام ، هل تشعر أن ذوقك قد زاد أو انخفض في حدته منذ جراحة إنقاص الوزن؟								س20
Q21	In your opinion, does loss of taste lead to better weight loss?									Yes	No	لا	نعم	برأيك هل فقدان التذوق يؤدي إلى إنقاص أفضل للوزن؟								س21
Q22	Is your postoperative change in taste greater or less than what you expected preoperatively?									Greater	Lesser	أقل	أكبر	هل تغير مذاقك بعد الجراحة أكبر أم أقل مما كنت تتوقعه قبل الجراحة؟								س22
Q23	How important is taste to the enjoyment of food?									Important	Not important	غير مهم	مهم	ما هي أهمية التذوق للاستمتاع بالطعام؟								س23

استبيان قياس الشهية
Council on Nutrition Appetite Questionnaire (CNAQ)

A. My appetite is 1. Very poor 2. Poor. 3. Average 4. Good 5. Very good	أ. شهيتي 1 . ضعيفة جدا 2 . ضعيفة . 3 . متوسط 4 . جيدة 5 . جيد جدا
B. When I eat, I feel full after 1. Eating only a few mouthfuls 2. Eating about a third of a plate/meal 3. Eating over half of a plate/meal 4. Eating most of the food 5. Hardly ever	ب. عندما أتناول الطعام ، أشعر بالشبع بعد : 1 . تناول بضع لقمات فقط 2 . تناول حوالي ثلث طبق / وجبة 3 . تناول أكثر من نصف طبق / وجبة 4 . تناول معظم الطعام 5 . نادرا
C. I feel hungry 1. Never 2. Occasionally. 3. Some of the time 4. Most of the time 5. All of the time	ج. أشعر بالجوع 1. أبدا 2. من حين لآخر. 3. بعض الوقت 4. معظم الوقت 5. في كل وقت
D. Food tastes 1. Very bad 2. Bad. 3. Average 4. Good 5. Very good	د. الأذواق الغذائية 1 . سيء جدا 2 . سيئ. 3 . متوسط 4 . جيد 5 . جيد جدا
F.Normally, I eat 1. less than one meal a day 2. One meal a day 3. Two meals a day 4. Three meals a day 5. More than three meals a day (including snacks)	ر. عادة ، انا أكل 1 . أقل من وجبة واحدة في اليوم 2 . وجبة واحدة في اليوم 3 . وجبتين في اليوم 4 . ثلاث وجبات في اليوم 5 . أكثر من ثلاث وجبات في اليوم (بما في ذلك الوجبات الخفيفة)
G. I feel sick or nauseated when I eat 1. Most times. 2. Often 3. Sometimes 4. Rarely. 5. Never	ز. اشعر بالغثيان او الغثيان عندما أكل 1 . معظم الأوقات. 2 . في كثير من الأحيان 3 . في بعض الأحيان 4 . نادرا. 5 . أبدا
H. Most of the time my mood is 1. Very sad 2. Sad 3. Neither sad nor happy 4. Happy 5. Very happy	ط. مزاجي معظم الوقت 1 . حزين جدا 2 . حزين 3 . لا حزين ولا سعيد 4 . سعيد 5 . سعيد جدا

Scoring: Total the score by adding the numbers associated with the patient's response. A score of less than 28 is cause for concern. If the total is 8-16 The patient is at risk for anorexia and needs nutrition counseling. 17-28 The patient needs frequent reassessment. >28 The patient is not at risk at this time.

استبيان قياس الإحساس بالجوع والشبع
Feel of hunger and fullness questionnaire

Subject code _____ **Trial**_____
Date _____/_____/19____ **VAS number** _____

Please make a vertical mark through the horizontal arrow to show how you feel at the moment. Left and right extremes represent minimum and maximum values respectively.

يرجى وضع علامة عمودية عبر السهم الأفقي لإظهار ما تشعر به في الوقت الحالي، يمثل أقصى اليسار واليمين القيم الدنيا والقصوى على التوالي.

أنا لست جائع على الاطلاق. I am not hungry at all	**ما مدى شعورك بالجوع؟** **How hungry do you feel?**	لم اشعر بمثل هذا الجوع من قبل I have never been more hungry
لا اشعر بالشبع على الاطلاق I am completely empty	**ما مدى رضاك؟** **How satisfied do you feel?**	لا أستطيع أكل لقمة اخرى I cannot eat another bite
لا أشعر بالشبع ابدا Not at all	**ما مدى شعورك بالشبع؟** **How Full do you feel?**	اشعر بأني ممتلئ جدا Totally full
جدا ضعيفة Very weak	**ما مدى رغبتك في الاكل؟** **How strong is your desire to eat?**	جدا قوية Very strong
لا شيء اطلاقا Nothing at al	**ما هي كمية الأكل التي تعتقد أنك تستطيع أكلها؟** **How much do you think you can eat?**	الكثير A lot

Consent statement	بيان موافقة و إقرار
I hereby confirm that all aspects related to the study have been explained to me including aims and procedures and that the study (does/does not) include any experimental therapies and that my participation is voluntary with no extra-expenses and there (is/is no) payment offered to me for participation. I have been given a copy of data related to the study and a copy from this consent.	أقر أنا الموقع أدناه أنه قد تم شرح كل ما يتعلق بالدراسة لي شاملا أهدافها و إجراءاتها وأنها(تتضمن/ لا تتضمن) أي علاجات تجريبية وأن مشاركتي تطوعية/اختيارية وأنه لن تترتب على المشاركة أية نفقات إضافية علي كما أنه (يوجد/ لا يوجد) مقابل مادي للمشاركة. وقد تم إعطائي نسخة من المعلومات المتعلقة بالدراسة ونسخة من هذا الإقرار.
Name of Research Participant:	**إسم المشارك في البحث:**
Signature of the participant:	**توقيع المشارك:**
Date of consent*(To be personally dated by the participant)*	**تاريخ الموافقة بعد التبصير***(يكتب المريض التاريخ بنفسه)* :
Name of the participant's legal guardian and relation (if applicable)	**اسم الولي القانوني علي المريض و صلة القرابة***(إن وجد)*
Signature of the participant's legal guardian (if applicable)	**توقيع الوصي القانوني علي المريض***(إن وجد)*
Date of the consent*(personally dated by the participant's guardian if applicable)*	**تاريخ الإقرار***(يكتب بواسطة الوصي القانوني على المريض إن وجد)*
Name of the Principal Investigator *(or delegate)*	**اسم الباحث الرئيسي** *(أو من ينوب عنه)*
Signature of the Principal Investigator *(or delegate)*	**توقيع الباحث الرئيسي***(أو من ينوب عنه)*
Date of the consent *(To be personally dated by the Principal Investigator or delegate)*	**تاريخ الإقرار** *(يكتب التاريخ بمعرفة الباحث الرئيسي أومن ينوب عنه)*
Name of the witness *(if applicable)*	**اسم الشاهد** *(إن وجد)*
Signature of the witness *(if applicable)*	**توقيع الشاهد***(إن وجد)*
Date of the consent *(To be personally dated by the witness)*	**تاريخ الإقرار***(يكتب التاريخ بواسطة الشاهد)*

Appendix 5: Ethical approval

مدينة الملك عبد الله الطبية
KING ABDULLAH MEDICAL CITY IN HOLY CAPITAL

المملكة العربية السعودية Kingdom of Saudi Arabia
وزارة الصحة Ministry of Health
مدينة الملك عبد الله الطبية بالعاصمة المقدسة King Abdulla Medical City in Holy capital
اللجنة المحلية لأخلاقيات البحث Institutional Review Board

Institutional Review Board Opinion Letter

Protocol Title	The Effect Of Zinc Deficiency In Taste Change Following Bariatric Surgery
Version	1.0
Principal investigator	Dr. Aly Elbahrawy
IRB number	20-719
Sponsor	NA

Dear Dr. Aly Elbahrawy,

This is to inform you that the above mentioned proposal has been the subject of expedited review by KAMC IRB registered at the National BioMedical Ethics Committee, King Abdulaziz City for Science and Technology on 14-07-1433 (Registration no. H-02-K-001) and is following the GCP-ICH regulations (OHRP Registration no. IORG0007625).

The decision for **expedited review** was based on the following submitted documents:

1. The protocol (version 3.0)
2. Informed Consent (version 1.0)
3. Questionnaire (version 1.0)

The opinion of the IRB is to **approve** this proposal with its current design:

- The study is approved for one year from the date of this letter. Extension can be requested one month before the expiry of the approval.
- To conduct research as per the approved documents
- Amendments to the approved documents require IRB approval before implementation
- End of study report is expected before expiration of approval
- The study conduct may be subject to audits by KAMC Human Research Protection Program (HRPP)
- Research participant confidentiality should be protected at all times and may be subject to audits by KAMC HRPP
- Document retention: all study documents should be kept by the principal investigator for a period of three years from study completion

General Approval conditions:

- **If your study involves participants consent: Copy of all consents should be submitted to IRB**
- **Final manuscript should be acknowledged by IRB before Journal Submission**
- **If patient's clinical photo would be used for publication or presentation additional patient consent will be required and should be submitted to IRB before publication.**

N.B.: Please note that this letter gives you ethical clearance to perform your study according to the approved documents but you will still need to obtain necessary administrative approval from the site/s where the study will be conducted.

Dr. Saad Saeed Alghamdi		**14-Feb-2021**
(Name of IRB Chair)	*(Signature)*	*DD/MM/YYYY (Date of approval)*

Institutional Review Board Opinion Letter

Protocol Title	The Effect Of Zinc Deficiency In Taste Change Following Bariatric Surgery
Version	2.0
Principal investigator	Dr. Aly Elbahrawy
IRB number	20-719
Sponsor	NA

Dear Dr. Aly Elbahrawy,

This is to inform you that the above mentioned proposal has been the subject of review by KAMC IRB registered at the National BioMedical Ethics Committee, King Abdulaziz City for Science and Technology on 14-07-1433 (Registration no. H-02-K-001) and is following the GCP-ICH regulations (OHRP Registration no. IORG0011096).

1. The decision for **expedited review** was based on the following submitted documents:
   - The protocol (version 3.0)
   - Informed Consent (version 1.0)
   - Questionnaire (version 1.0)
2. Extension request submitted on **09-Mar-2022** Based on following documents:
   - Progress Report for prospective and cross-sectional Studies. (Dated 01-Mar-2022)
   - Application for IRB Approval of Research Amendment. (Dated 09-Mar-2022)

The opinion of the IRB is to **approve** extension of this proposal with its current design:

- The study is approved for one year from the date of this letter. Extension can be requested one month before the expiry of the approval.
- To conduct research as per the approved documents
- Amendments to the approved documents require IRB approval before implementation
- End of study report is expected before expiration of approval
- The study conduct may be subject to audits by KAMC Human Research Protection Program (HRPP)
- Research participant confidentiality should be protected at all times and may be subject to audits by KAMC HRPP
- Document retention: all study documents should be kept by the principal investigator for a period of three years from study completion

General Approval conditions:

- **If your study involves participants consent: Copy of all consents should be submitted to IRB**
- **If patient's clinical photo would be used for publication or presentation additional patient consent will be required and should be submitted to IRB before publication.**

N.B.: Please note that this letter gives you ethical clearance to perform your study according to the approved documents but you will still need to obtain necessary administrative approval from the site/s where the study will be conducted.

Dr. Osama E. Shams		**31-Mar-2021**
(Name of IRB Chair)	*(Signature)*	*DD/MM/YYYY (Date of approval)*

Appendix 6. Search strategies of the systematic review and meta-analysis of randomized controlled trials (chapter 5).

PubMed search strategies are as follows. (“taste disorders” (MeSH Terms) OR taste disorder (Text Word)) OR (“taste” (MeSH Terms) OR taste (Text Word)) AND change (All Fields)) OR (“taste” (MeSH Terms) OR taste (Text Word)) AND disfunction (All Fields)) OR (“dyspepsia” (MeSH Terms) OR dyspepsia (Text Word) AND (“zinc” (MeSH Terms) OR zinc (Text Word)) OR (“zinc” (MeSH Terms) OR zinc (Text Word)).

Appendix 7: Ethical approval (Chapter 6).

NHS
Health Research Authority

East Midlands - Derby Research Ethics Committee
Equinox House
City Link
Nottingham
NG2 4LA

Tel: +442071048276

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

19 November 2021

Dr. Arash Ardavani
7-11 Brook Street, Darley Bank
Derby
Derbyshire
DE1 3PF

Dear Dr. Ardavani

Study title:	**Exploring the immediate and short-term effects of a very low calorie diet (VLCD) with and without adjuvant exercise training on lean body mass (LBM), vascular function, metabolic health and muscle protein synthesis (MPS) in overweight diabetic individuals.**
REC reference:	**19/EM/0227**
Protocol number:	**19026**
Amendment number:	**SA03 19026**
Amendment date:	**05 October 2021**
IRAS project ID:	**255016**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [Completed Amendment Tool]	1.5	05 October 2021
Other [Tabled Response+v2.1+12.11.21]	V2.1	12 November 2021
Other [Ethics Amendment Log Summary Final Version 1.3 12.11.21]	V1.3	12 November 2021
Participant information sheet (PIS) [INFO+SHEET+Final+Version+2.8+18.11.21.doc]	V2.8	18 November 2021
Research protocol or project proposal [PROTOCOL+Interventional+Final+Version+3.9+12.11.21]	V3.9	12 November 2021
Validated questionnaire [Modified Dukes Activity Status Index]	1.0	13 September 2021
Validated questionnaire [36-item Short-Form (SF-36) Questionnaire]	1.0	13 September 2021

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 255016:	Please quote this number on all correspondence

Yours sincerely



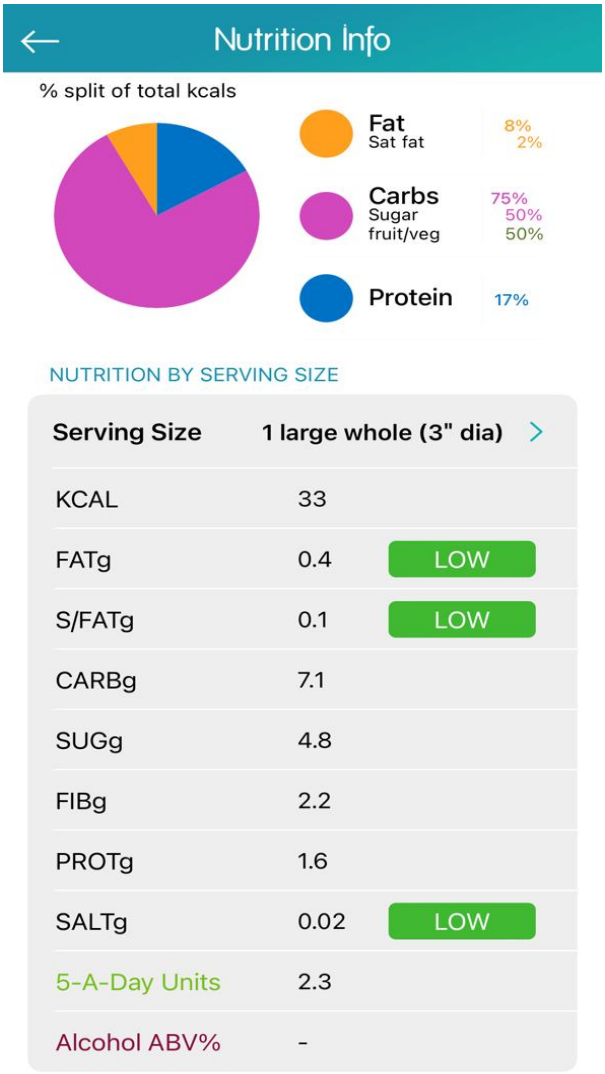
Ms Margret Vince
Meeting Chair

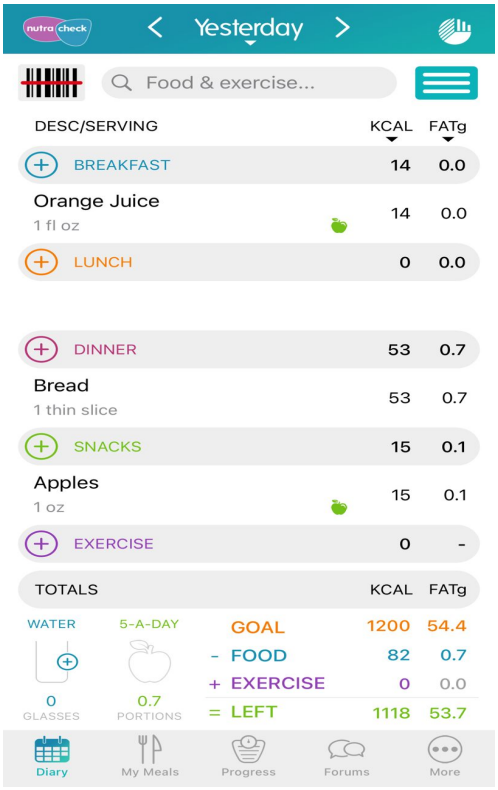
E-mail: derby.rec@hra.nhs.uk

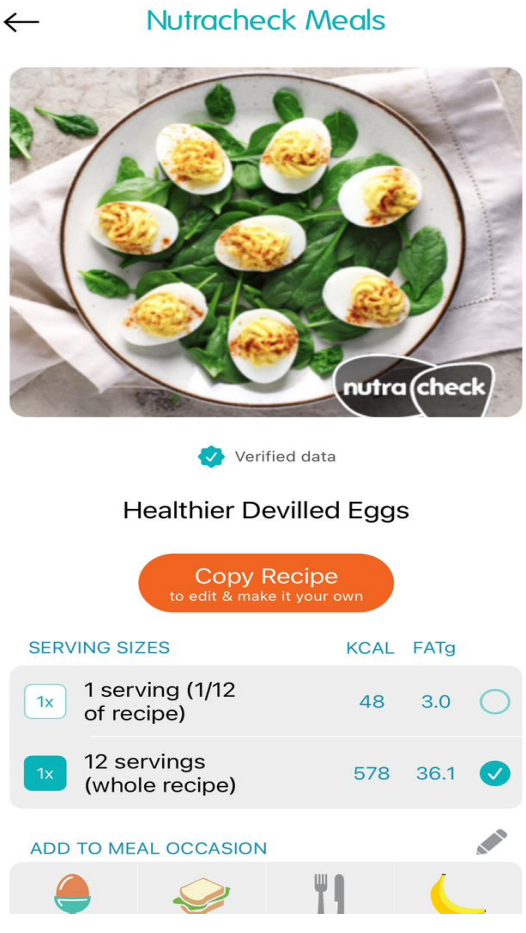
Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr. Arash Ardavani*

Appendix 8: Nutracheck App.







Nutracheck provides clients with personalised insights regarding their food choices and eating habits by monitor food intake without adhering to a specific diet or intricate points system. The app provides users with the calorie and nutritional content of meals.

Appendix 9: Additional calorie sources

IRAS: 255016

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VLCDeXDM: Additional Calorie Sources

In addition to the 600kcal provided by the very low calorie meals, all participants in this trial are to consume a further 200kcal of extra food.

As stated in the Diet Diary that you have (or are yet to) receive a copy of, this additional 200kcal should come from

The following vegetables and nuts come to approximately 100kcal.

Therefore, you're welcome to consume any paired combination (or double of any of the following) on a daily basis:

Vegetables	**Nuts**
1 medium sweet potato (33g)	14 almonds
Potato (77g) (4/5 of a small potato)	8 halved walnuts
Carrots (250g) (4 medium carrots)	10 cashews
3 large tomatoes	29 pistachios
1 cup of green peas (140g)	11 hazelnuts
2 medium onions	11 pecans
2 heads of lettuce	6 macadamias
1 medium egg plant	3 brazil nuts
2 cucumbers	
1 large ear of corn	
2 large red bell peppers	
12 brussels sprouts	
20 large mushrooms	
400g cauliflower	
140g peas	
240g sugarsnap peas	
400g aubergine	

We have provided a working example below:

Monday	6 large tomatoes
Tuesday	3 large tomatoes; 14 almonds
Wednesday	28 almonds
Thursday	2 cucumbers; 11 pecans
Friday	140g peas; 14 almonds

Standalone document for dissemination to enrolled participants
Created by: Georgina Carolan
Modified by: Arash Ardavani