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Research Article

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Failure to Thrive: A Review for a Relationship between Coeliac Disease and Obesity

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Summary

Objectives: *The primary objective of this review was to provide a systematic review of the literature on the relationship between CD and obesity. Further, the reviewer had the purpose of conducting an investigation on this correlation, ranging from pediatrics to adults, in specific areas such as the mechanism of the two conditions and the nutritional interventions. The mechanism review involved finding any pathogenic and pathophysiological link between the two conditions and investigating the possible association in clinical evidence and manifestations and of the symptoms. As a result, the present research was designed to establish a paper that can effectively inform not only the public but health care providers, concerning the importance of proper and time-sensitive diagnosis.*

Methods: *In order to achieve these objectives, the researcher conducted desk-based research, which involved a comprehensive review of numerous journal articles drawn from various publishers. The search strategy involved the use of both internal and external secondary sources of information obtained from Science Direct, PubMed, Journal of Paediatric Gastroenterology and Nutrition, The American Journal of Clinical Nutrition, and The European Journal of Clinical Nutrition, among others. Moreover, the search strategy also considered the mechanistic pathology, functional physiology, and human intervention.*

Results: *The key pathophysiological findings indicated that CD and obesity have a connection in the context of the predisposing factors, which are genetic, environmental and immunological factors. Further, the two conditions also show connection in the aspects of human nutritional interventions, where the intervention for CD was established to involve a GFD, however, some patients have been recorded as becoming obese once they start the treatment process.*

Conclusion: *Conclusively, it was important establishing a link between obesity and CD based on the clinical implications of the findings, as well as the general healthcare field; where, the present paper points out for the proper diagnosis of both conditions, whether the symptoms are atypical or not. Hence, it was important to provide a precise nutritional intervention for future patients, which may involve an introduction of a GFD before diagnosis, and strict follow-up and education for the patients on the importance of this intervention.*

List of Abbreviations

AIP: Autoimmune Protocol Diet
BMI: Body Mass Index
CD: Coeliac Disease
GF: Gluten-free
GFD: Gluten-free Diet
HLA: Human Leukocyte Antigen
IgA: Immunoglobulin A
NSAIDs: Non-steroidal Anti-inflammatory Drugs
tTG: Tissue Transglutaminase
WHO: World Health Organization

Glossary

BMI A system used to categorise individuals into "underweight", "normal weight", "overweight" and "obese"

Dermatitis

Heretiformis: An intensely itchy and blistering skin disorder linked with CD Epithelial cell Skin cells

Genetic

Pre-disposition: An individual's susceptibility to genetic diseases, disorders, etc.
Gliadin: Protein found in wheat
Glutamine: An amino acid used in the biosynthesis of proteins
GFD: A diet that specifically excludes any and all wheat products, such as barley, rye

HLA DQ2

Genotype: The gene carried by most diagnosed with, or at risk for, CD

HLA DQ8

Genotype: The gene few diagnosed with, or at risk for, CD
Hypoglycemia: Low levels of glucose in the blood – low blood sugar
IgA Antigliadin: Produced in response to gluten and prolamines
Malabsorption: Under absorption of nutrients, specifically through the small intestine

Malnutrition: A combination of malabsorption & micronutrient deficiencies

Micronutrient

Deficiencies: Vitamin & mineral deficiency

Pathogenetic: Various bacteria, viruses, etc. that cause disease

Pathology: Diagnosis of disease

Prolamine: Plant storage proteins found in seeds of cereal grains such as,wheat, barley, rye and corn

Physiology: How living organisms function

Salience

Hierarchy: Ranking system based on prominence and importance

Tissue

Transglutaminase: Calcium dependent universal enzyme which catalyses Post-translational modification of proteins and is released from cells during inflammation

tTG antibody: Primary blood test for diagnosis of CD

Villi: Finger-like, micronutrient projections found in the small intestine, which absorb nutrients.

Villous: Atrophy Damage done to the villi

Introduction

Background

Coeliac Disease is one of the most common chronic illnesses in childhood and, in 2007, was estimated to effect one in every 133 Canadians [1,2]. This illness is a life-long autoimmune condition, which affects not only the stomach, small intestine, large intestine and bowels, but neurological and psychological states as well [1,3]. Once considered a malabsorption syndrome found strictly in childhood, CD is now recognized as a multi-system disorder [4].

Previously, CD has been characterized with severe weight loss and "failure to thrive", predominantly in children. According a report from Autoimmunity Reviews, CD has been classified as a lifelong autoimmune condition that is prompted by a child's intolerance to gluten [5]. Further, a report on CD in the European Journal of Paediatrics, by Kneepkens & Von Blomberg established that the condition severely limits the absorption of nutrients in the intestinal tract due to damage of the villi, making it difficult for children to grow and prosper [6].

Moreover, Balamtekin et al. (2010) indicated that because CD is an immune mediated inflammatory condition, it affects the small bowel mucosa, which results from a genetic intolerance to gluten-derived peptides (gliadins) of that found in rye, barley, and wheat [7,8]. However, more recent studies have been reporting gripping correlations between CD and obesity, in both adults and children [9,10].

Although the term "failure to thrive" has typically been used to describe the typical or 'classic' outward symptoms associated with malab sorption of nutrients and severe micronutrient deficiencies, hence, poor growth in children, it can also be used to describe malnutrition and malab sorption, and subsequent intestinal damage from misdiagnosis or late-diagnosed CD, especially among the adult community as well as those who have been identified as overweight or obese [11-14].

Notably, whether the individual is overweight, obese or underweight, "failure to thrive" is still a very real issue, as "overweight" or "obese" does not mean that the individual is thriving or flourishing nutritionally, which is precisely why so many overweight and obese individuals with CD are being overlooked [11,15].

Further more, as this autoimmune condition has such drastic and different outward symptoms for each individual, it can often be discounted and undiagnosed, consequently leading to greater inflammation and damage and therefore contributing to a much higher risk for other diseases and autoimmune conditions, such as rheumatoid arthritis and cardiovascular disease [15,16].

While CD can be diagnosed and developed at any age, more recent studies are revealing the misdiagnosis and prevalence surrounding obesity and overweight individuals with CD [11]. The global prevalence of the disease has been shown to range from between one and two per cent, where the presentation of CD has significantly changed over the years; whereby, in the last twenty-five years, the most notable symptoms, such as malab sorption and diarrhoea have radically reduced during the onset of the disease in both children and adults, making this disease even more difficult to diagnose at the onset [14,17]. Likewise, the atypical presentation of the disease has been reported to have significantly increased [18].

Previously, the micronutrient deficiency symptoms of CD, such as anemia, meant weight loss and frail body types, however, studies are now showing more research towards overweight and obese individuals with the same micronutrient deficiencies [18]. Therefore, the continued differences in presentation or manifestation of the disease in both children and adults indicate a critical aspect in the misdiagnosis and correlation of the disease with obesity; thus, some recent studies have tried to investigate clinical presentations of the two conditions. Overall, it was important investigating the possible relationship between CD and obesity, based on the burden of the illnesses, and the rising incidences and prevalence throughout the world.

Aims and Objectives

The main aim of the present research was to provide a systematic review of the literature on the link between CD and obesity. This review was aimed at investigating a relationship concerning CD and obesity, ranging from pediatrics to adults. Although CD has not been specifically associated with overweight or obese individuals in the past, the present research appreciates the fact that more recent studies are supporting this trend, possibly due to severe inflammation, malnutrition, and a gluten-rich lifestyle. As a result, this review focused on the symptoms and effects of CD and how they may promote weight gain and obesity through a 'domino effect' of one symptom leading to another, concentrating on inflammation, diet, and lifestyle, as well as specific nutritional interventions. Similarly, the central concerns in this review include the pathogenesis and clinical evidence of a connection concerning CD and obesity in children and adults.

Moreover, it was important to expose any causes and main clinical factors that could be linked to both conditions at diagnosis level, which is essential to medical practitioners for providing an accurate diagnosis. Furthermore, the present review aimed at clarifying if gluten withdrawal may affect the standard pattern and trend of the nutritional status of CD patients and the comparison drawn to obesity cases. Overall, this research will contribute to the nutritional research that can help in medical interventions in cases of obesity and CD; thus, reducing the overall wastage of resources, as well as the misdiagnosis and interventions in cases of the two conditions in an individual.

- To determine a connection in the presentation of CD and obesity in both Children and adults.
- To investigate the link in clinical evidences and manifestations, and the symptoms of CD and obesity in children and adults as reported in the literature.
- To ascertain the pathogenic and pathophysiological link between obesity and CD.
- To establish the similarity and difference in previous relevant reports on any association between obesity and CD.

Methodology

Search Process

This section presents the review design and the data collection strategies that were adopted to conduct this systematic literature review. The subsequent sections show how the systematic review and meta-analysis were conducted to evaluate the possible relationship between CD and obesity as researched and presented in previous research, studies and health reports. The specific aspects of the search process contained in this section are the search strategy, mechanistic pathology search strategy, functional physiology search strategy, and the human intervention search strategy.

Review Search Strategy

In the review, the search strategy refers to a structured organization of terms that were used in a review and shows how those terms combined in order to accurately access quality results [19]. Similarly, in order to conduct a comprehensive and explorative review, the researcher chose a desk-based research method as the most appropriate method to review the relevant past reports in the context of the present study.

Notably, the present review adopted both internal and external secondary sources of information; where the internal sources were mostly the preferred sources due to the authenticity and precise information they contained. Otherwise, it was important for the review to be performed using both the external and internal secondary sources as to have comprehensive research.

Importantly, desk-based research was established to be useful for the present review due to the ease of access to the secondary sources of data, their availability, and the possibility of obtaining much of the relevant information from the secondary sources. To obtain relevant information from the secondary sources, there were inclusion and exclusion strategies that were used in the selection of appropriate journal papers that were reviewed. The inclusion and exclusion criterion were adopted to avoid 'cherry picking'.

Notably, the secondary sources reviewed were carefully examined for both credibility and validity of the information contained in those sources. The relevant papers were considered as a paper summary or an abstract, which were used in the selection of the relevance of the paper. Further, the papers were assessed for the year of publication; whereby, information that was published between 2000 and 2016 were considered top sources for the review.

However, some sources were still considered relevant if the paper included information that was not accessible in more current publications; a few publications from 1969-2000 provided necessary information, history and statistics on CD and obesity. Moreover, there were specific keywords used to enhance the search of the paper from the primary databases, PubMed, Science Direct and the European Journal of Clinical Nutrition searches for CD and obesity.

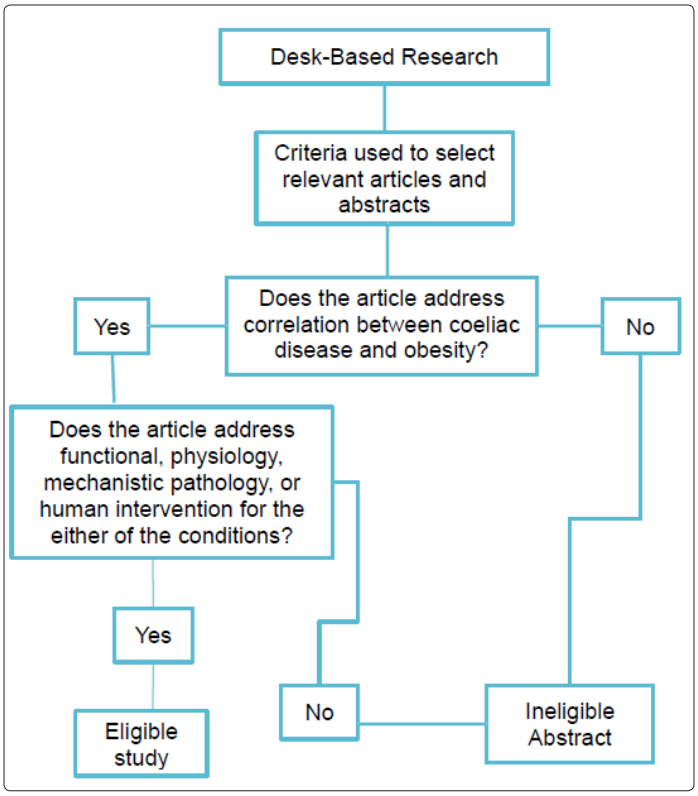

Figure 1: The Flow Chart for the Inclusion and Exclusion Criteria

The flow chart above guided the use of the search terms that were developed for this review. The inclusion and exclusion criterion helped where the search process of the review papers was the initial step, which was followed by the search for mechanistic evidence and lastly, the primary literature in humans. Further, there was the review of nutritional interventions.

Moreover, the reviewer considered the quality of the studies in terms of the evidence and salience hierarchy. The total numbers of papers were 10, where the review was given 20 per cent, mechanistic and intervention evidence was given 40 per cent each.

The search words were developed based on the key variables in the review topic; CD and Obesity. The reviewer used the keyword correlation to ascertain the relevance of the papers. Moreover, the other strategy that was used to collect the search words involved the analysis of the frequency of the words such as, celiac and obesity in the title, keywords, and the abstract in the articles published in the chosen databases.

Mechanistic Pathology Search Strategy

In the context of mechanistic pathology, the search strategy considered specific guidelines and checklists that were used to assess the relevant journal papers from the databases. Notably, in this section, the animal research that was reviewed considered the nature of CD and obesity. Further, the review of the previous studies considered three elements; In Vitro, Animal, and Human experiments.

Functional Physiology Search Strategy

In this section, the search strategy involved establishing normal functional physiology. A sensitive search found that the proportion of articles had experiments conducted about the physiology of the humans; particularly, children in the context of obesity and CD. Moreover, the specialists were consulted on the validity and authenticity of the information presented in the articles or studies carried out on the functional physiology of children having either obesity or CD.

Human Intervention Search Strategy

This search strategy was based on points of nutritional intervention that were identified in the journals listed in the database. The strategies that have been used to correct obesity in humans were reviewed alongside the intervention and management strategies for CD; hence, the relationship between the intervention strategies for the two conditions was established. Moreover, the analysis of the interventions was conducted to ascertain the frequency of the journal papers reporting similar strategies. Further, the authenticity of the interventions was measured against the suggestions made by nutritionists on how obesity and CD are corrected and/or managed in humans.

Results

Synopsis (Part A)

In this section, the mechanism review process and the nutritional intervention strategies are presented.

Table 1: The Mechanism Review

Topics Considered:	Studies Reviewed:
Evidence of the Relationship in Mechanism for CD and Obesity (3.2.1.1)	Sing et al. (2016). This study formed the foundation of the subsequent review sections based on the report. Pals et al. 2014
Pathogenetic Link Between CD and Obesity (3.2.1.2)	Balamtekin, Loots, et al. 2011; Stephan C Bischoff et al. 2014; Brar et al. 2007; Czaja-Bulsa et al. 2001; Diamanti, Capriati, Basso, Panetta, Laurora, et al. 2014; Furse & Mee 2005; Green et al. 2015; Murray et al. 2008; Ng et al. 2013; Olén et al. 2009; Rodríguez-Almagro et al. 2016; Stein & Schuppan 2014; Venkatasubramani et al. 2010 (Fasano 2011; Marsh 1992)
Relationship of CD and Obesity in terms of BMI, including the Effect of Gluten Withdrawal on Obese CD Patients (3.2.1.3)	(Cheng et al. 2010) Dickey et al. 2006; Kabbani et al. 2012
Prevalence of Obesity in CD Patients (3.2.1.4)	Brambilla et al. 2013; Icaza-Chavez 2014; Norsa et al. 2013; Reilly et al. 2011b; Valletta et al. 2010b; Venkatasubramani et al. 2010 (Barera et al. 2000)
Relationship between CD, Obesity and Liver Disease (3.2.1.5)	Abdo et al. 2004; Aurangzeb et al. 2010; Balamtekin et al. 2010; Brambilla et al. 2013; Capriati et al. 2016; Dickey et al. 2006; Fasano 2005; Hunt & van Heel 2009; Hypponen et al. 2000; Kelly et al. 2015; Lamacchia et al. 2014; Leffler et al. 2015; Mokdad AH et al. 2003; Nejad et al. 2011; Norsa et al. 2013; Phatak & Pashankar 2015; Reilly et al. 2011a; Telega et al. 2008; Venkatasubramani et al. 2010; Zali et al. 2011
Heredity of CD and Obesity (3.2.1.6)	Alexander et al. 2010; Dieli-crimi et al. 2015; Freeman 2012; Hunt & van Heel 2009; Katzmarzyk et al. 2000; Leivers et al. 2014; McCrae 1969; S O'Rahilly & Farooqi 2008; van Heel et al. 2005; Visser 2010; Wolters & Wijmenga 2008; Zhernakova & Wijmenga 2008 (Ho & MacKenzie 1999; Voight et al. 2006)
Pathophysiological Findings for Obesity and CD (3.2.1.7)	Alexander et al. 2010; Leivers et al. 2014; Liu et al. 2014; Murray 1999; Stein & Schuppan 2014; Yang et al. 2014 (Dickson et al. 2006; Withoff et al. 2016)
Analysis of the Reports and Methodology Used in Establishing a Relationship between CD and Obesity (3.2.1.8)	Aurangzeb et al. 2010; Bailey & Ferro-Luzzi 1995; Brambilla et al. 2013; Cawley & Burkhauser 2006; Diamanti, Capriati, Basso, Panetta, Laurora, et al. 2014; Dickey et al. 2006; Kapoerchan et al. 2010; Sollid & Khosla 2012; Pals et al. 2014; Valletta et al. 2010b; van Heel et al. 2005 (Dietz & Bellizzi 1999; Reilly et al. 2011a)

Table 2: Nutritional Intervention Table

Topics Considered:	Studies Reviewed:
Use of Human Support for Interventions (3.2.2.1)	Campbell 2014; Capristo et al. 2000; Clifton et al. 2008; Frassetto et al. 2009; Gottfried 2016; Hinney et al. 2010; Kupfer et al. 2012; Kupper 2005; Lau et al. 2007; Martínez 2014; Pinier et al. 2010; Rubio- Tapia et al. 2010; See & JA 2006; Soares et al. 2013; Vilppula et al. 2011; Witkow et al. 2008 (Kussmann & Fay 2008)
Withdrawal of GFD and the possible Effects on Obese CD Patients (3.2.2.2)	Aurangzeb et al. 2010; Barera et al. 2000; Diamanti, Capriati, Basso, Panetta & Francavilla 2014; Ludvigsson et al. 2015; Sanchez-Albisua et al. 2005; Valletta et al. 2010b (Mooney et al. 2014; Nóvoa Medina et al. 2008)
Mandatory Nutritional Follow-Up after Diagnosis in the case of CD and Obesity (3.2.2.3)	Diamanti, Capriati, Basso, Panetta & Francavilla 2014; Dickey et al. 2006; Valletta et al. 2010b (Dickson et al. 2006)

The reviewed reports were mostly obtained from PubMed, Science Direct, Google Scholar, The Journal of Pediatrics and Child Health, Journal of Pediatrics Gastroenterology and Nutrition, and The European Journal of Nutrition.

Key pathophysiological findings

In the review of the pathophysiological findings, it was important to establish that several studies have been conducted based on the three main processes that predispose an individual to either CD and/or obesity. Notably, many of the reviewed journals indicated that genetic predisposition to the condition, environmental factors, and immunologically based inflammations are the key processes that determine the prevalence and incidences of CD among various populations [20]. Further, it was important noting that the genetic factors that have been associated with CD are similar to the ones that predispose an individual to becoming overweight or obese. Specifically, the HLA DQ2 and DQ8 genotypes were established to be critical in presenting the possible relationship among obesity and CD [21].

Moreover, genetic predisposition was found to have a significant influence on various populations as it determines the prevalence of both obesity and CD amongst children and adults. Furthermore, the genetic factors indicated that the two conditions could be passed from one generation to another, based on the degree of relationships.

Summary of clinical implications and applications

Various elements were reviewed to help identify the possible link between the clinical importance of obesity and CD. It was necessary to review the literature on a wide spectrum of GFDs as a nutritional intervention strategy to help manage CD, including go there strategies that could help to control both obesity and CD. Notably, the PubMed and Science Direct searches for GFD ensured that relevant papers were reviewed and a proper consensus among authors was achieved. It was also important noting that the authors agreed on the need for introducing a GFD to ensure a controlled trial amongst CD patients.

Moreover, there was the call for efficient education of the patients as well as post treatment assessment, or observation, to ensure that the patients restrict their diet to a GFD. Patient education was a chief concern; where the dietician, nutritionist or physician should provide information about different variations of GFDs at the time of diagnosis. Various authors recommended a useful approach of offering a follow-up consultation after diagnosis so that the patients could be allowed to ask questions on issues that concern their health and diet. Such practices were recommended for both obese/overweight patients with CD.

Moreover, the clinicians should find the discoveries of this review useful in providing the strategies for effectively helping the populations with CD and obesity through nutritional interventions.

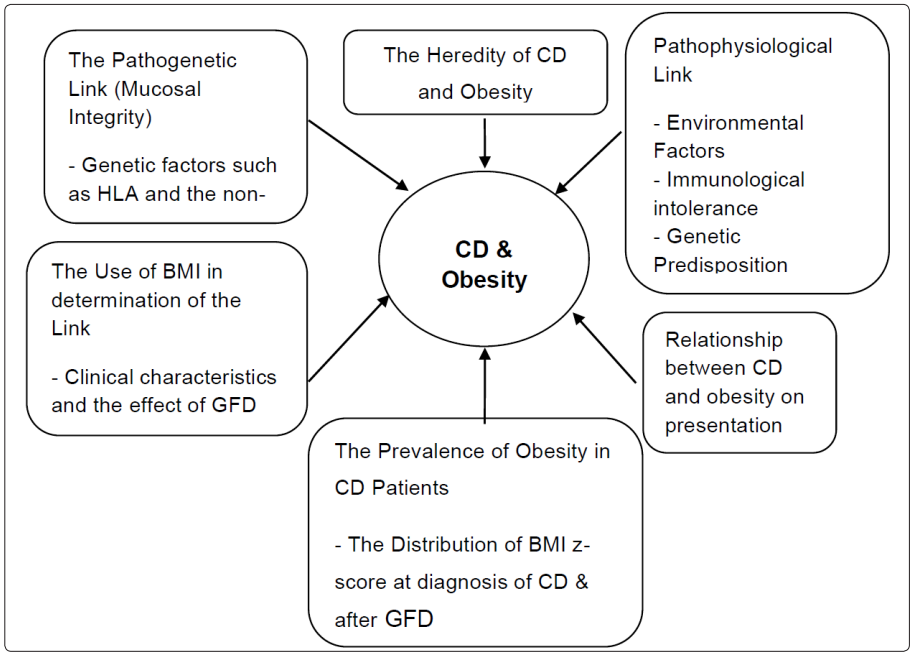

Diagram 1: Final Version of Mechanism Diagram

Analysis of Primary Research (Part B)

Evidence for a relationship in the mechanism of CD and obesity

In this section, the summary of the analysis of the previous primary studies has been presented. The section is divided into two subsections: the evidence of a relationship in the mechanism between CD and obesity, and points for nutritional intervention.

Summary of the main case reports

In this section, several publications were found useful in providing evidence for a relationship between CD and obesity, especially among children in the context of their mechanisms. The review of studies from PubMed, Science Direct and The European Journal of Clinical Nutrition presented accurate and authentic purpose that proved such correlation. A study conducted by Singh et al. demonstrated a link between the mechanism of CD and obesity as presented in children. In this study, Singh et al. reviewed data on the BMI of the study subjects (patients with CD) [18]. The researchers retrospectively studied case reports from a total of 210 children, as well as adult patients with CD. The BMI categories for this study were classified as "underweight", "normal weight", "overweight" and "obese" and they implemented the revised Indian Association of Pediatrics BMI-for-age charts for those subjects between 12 and 18 years. The results obtained from by Singh et al. indicated that; of the 210 patients used, 9.1 per cent were categorized as "overweight" and/or "obese" [18]. The symptoms of the disease that were measured included titer of anti-tissue transglutaminase antibody, frequencies of diarrhoea, anorexia and weakness, anemia, and severity of villous atrophy in those characterized as "underweight", "normal weight" or" overweight" [18].

Overall, this research demonstrated that, in practice, only a third of the patients with the CD reported low BMI, suggesting that 8 to 40 per cent of patients with CD are either overweight or even obese, therefore leaving a significant gap for this population within the CD community [18].

Concurrently, there were a few cases where the research was not comprehensive or precise enough to provide the specifics regarding the mechanisms for obesity and CD. Moreover, there are reports that show the BMI as an unreliable tool for predicting CD amongst children [2]. Otherwise, this study did provide a noteworthy insight into a small and significant relationship between CD and obesity, where the BMI provided a decent understanding of how the expression of these diseases, and weight of an individual, may vary.

Pathogenetic link between CD and obesity

There has been thorough research concerning three processes which, when brought together, are considered to result in CD [20,21]. These processes include environmental factors, genetic predisposition, and immunologically based inflammation [20]. In a report from Venkatasubramani et al., the clinical presentation of CD in children was noted to be variable and different with the age of the child, which implies that even the pathogenetic associations can vary with the age of the child [22,23]. Notably, the intestinal adaptation of the child consisted of morphological changes of the gut mucosa, which included increased illus height, epithelial cell number, and crypt depth [7,23].

Importantly, the report by Venkatasubramani et al. indicated that among CD patients, deterioration determines the loss of normal intestinal function; which can hypothetically induce increased absorption of the intestinal tract [22]. It is this overcompensation that can lead to the overall withdrawal of energy, which may exceed that which is required by the child; hence, there is the higher risk of increased weight, possibly leading to obesity [10,22].

Although there is still a significant relationship between CD and the classic presentation of underweight, there are, however, a small yet noteworthy number of cases that will present as overweight and sometimes even obese. According to a 2001 report from Czaja-Bulsa et al., children who are less than two years of age normally exhibit 'classic' presentations of CD, such as weight-loss, alongside malab sorption [24]. However, older children and adults can present more 'atypical' symptoms, such as weight gain [16]. Some of the 'classic 'symptoms of CD among children may result from lack of intestinal adaptation, which may be less developed among young children but prominent among the older ones [16,24]. However, studies by Brar et al. and Murray et al. indicated important and diverse views on parallels between the pathogenesis of CD and obesity among children [25,26]. Specifically, the authors indicated that there was no overwhelmingly apparent correlation between the presentation of CD and the degree of the atrophy among intestinal villi [25]. Further, Murray et al. indicated that the visualized intestine using the video endoscopic procedures does not show any correlation between the hypothetical atrophy of the intestinal villi and CD [26].

In this report, Murray et al. used 38 consecutive patients, who had untreated, biopsy-proven CD, to undergo the wireless capsule endoscopy [26]. The results of the study revealed that 35 of the subjects had visible deterioration, 20 of them exhibited signs of extensive enteropathy,12 showed limited enteropathy that was only on the duodenum, while only one patient showed jejunum enteropathy. Upon introduction of a GFD, Murray et al. indicated the pattern and extent of atrophy to have improved quantitatively and qualitatively [26]. Thus, the pathogenesis of CD was established to affect highly variable portions of the small intestine, which starts at the duodenum.

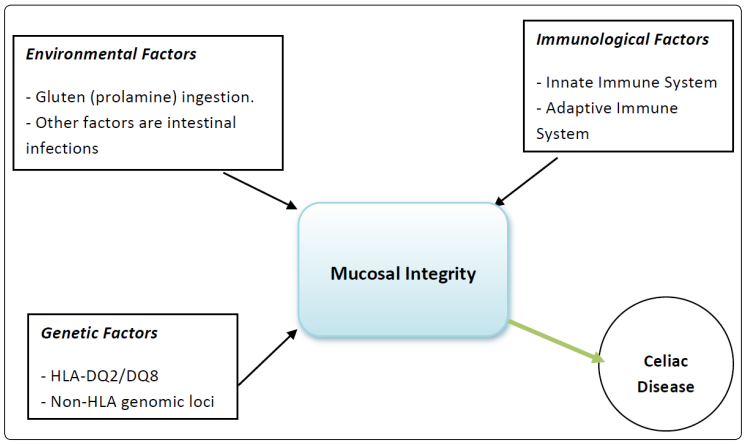

Diagram 2: The pathogenesis of CD indicating the Involvement of Environmental, Genetic and Immunological Factors

The above diagram indicates the pathogenesis of CD, which can be manifested at childhood or adulthood. Further, the a etiology of CD can be seen as that which is multi factorial and involves strong genetic susceptibility [27]. Overall, the studies reviewed in the context of the pathogenesis of CD and obesity aided in revealing some important correlations between the two aspects. Notably, CD may indeed develop among patients with obesity, which can reflect ones predisposition, such as the genetic, environmental, and nutritional factors [28,29]. Moreover, the symptoms of malab sorption have been established to manifest in obese patients at the onset of this disease, which may be a factor in the decreased prevalence of obesity in CD patients [10].

Relationship between CD and obesity in terms of BMI, including the effect of gluten withdrawal on obese patients

In order to better understand the change in BMI and how it may relate to those with CD, several studies conducted in the context of investigating the BMI and CD were reviewed. Firstly, Kabbani et al. conducted a comprehensive study on BMI and the risk of obesity in those with CD. Whilst conducting the study, the researchers appreciated that CD has been increasingly diagnosed and the weight changes have become common aspects after the adoption of a GFD [12]. The primary aim of the research done by Kabbani et al. was to assess the changes in BMI after an individual was diagnosed within a large CD population. Some of the information that was retrieved from this research included age and symptoms at diagnosis [12]. Further, the researchers reviewed, retrospectively, the electronic records of a total of 1018 persons with biopsy-confirmed CD [12]. Moreover, the initial and follow-up BMIs were recorded, as well as the GFD adherence, as assessed by an expert dietician [12]. The subjects were stratified in to two distinct groups of GFD adherence, which either involved adequate orinadequate adherence.

The results obtained by Kabbani et al. indicated important aspects on the relationship between CD and obesity. The most vital part of the results was on the effects of a GFD on BMI and how that related to CD [12]. Notably, the mean time that was established to be between the first and the last BMI was approximately three and a half years. Each patient's follow-up BMIs were also established to be statistically higher than the original BMIs; 65.5 per cent of the subjects who were underweight at the diagnosis, at the end of the study had attained a normal weight at the follow-up stage. However, 4.4 percent had been diagnosed as obese at the follow-up. The drop in the underweight subjects from the baseline to the follow-up was indicated to be statistically significant (from 6.8 per cent to 3.8 per cent). The Table below illustrates the excerpt of the results obtained from the changes at follow-up for the subjects by the BMI category [12].

Table 3: By convention, a BMI change of two points or greater was considered clinically significant

BMI change after diagnosis of CD				
BMI category	**<18.5**	**18.5–24.9**	**25–29.9**	**≥30**
Initial BMI (n = 679)	46 (6.8%)	416 (61.3%)	139 (20.5%)	78 (11.5%)
Follow-up BMI (n = 679)	26 (3.8%)	390 (57.4%)	164 (24.2%)	99 (14.6%)
P value	0.02	0.17	0.11	0.1
BMI increase ≥2 points	24/46 (52.2%)	88/416 (21.2%)	31/139 (22.3%)	17/78 (21.8%)
BMI decrease ≥2 points	1/46 (2.2%)	20/416(4.8%)	25/139(18.0%)	18/78(23.1%)
BMI change <2 points	21/46 (45.6)	308/416 (74%)	83/139 (59.7%)	43/78 (55.1%)

Further review of the results from Kabbani et al., indicated the comparison of a large CD population to those of the regional BMI data; this was aimed to better characterize the effect of CD on body weight within the CD population [12]. It was important noting that the weight gain on the GFD may be considered a positive for the patients who are underweight at diagnosis, where approximately 66 percent of the subjects had normal weight at follow-up. Moreover, the similar weight gain was indicated to be less favorable among the patients who began at normal or overweight at diagnosis, with roughly 21.5 per cent of patients having clinically significant weight gain, possibly leading to clinical obesity [12].

Other studies in supporting a relationship between CD and change in the BMI

A 2006 study conducted by Dickey and Kearney investigated the overweight community in CD, specifically, the clinical characteristics and the effects of a GFD. This research was found to be very similar to the results obtained by Kabbani et al. [12]. In their study, Dickey and Kearney considered the review of BMI measurements and various clinical and pathological characteristics of CD patients from a database of 371 who were diagnosed over a period of ten years [30]. The results of the study established the mean BMI as 24.6 kg/m^2.

The number of patients who were categorized as "underweight" was 17, 221 were "normal weight", 143 were "overweight" (with the BMI over 25), and 48 were considered "obese" (with the BMI ≥ 30.0) [30]. Overall, it was important obtaining that although many individuals with CD are underweight at diagnosis, research is now seeing a small, yet significant group of overweight and/or obese persons within the CD community. Thus triggering the notion that overweight or obese individuals should not be overlooked in the diagnosis of CD.

Prevalence of obesity in CD patients

Currently, there are few case series that have been published on this topic, however, there were some studies that attempted to reveal a specific linkage and prevalence of obesity among CD patients, as obesity has been linked to other digestive and gut disorders [31]. Valletta et al. reported the prevalence of obesity and overweight to be three and eleven percent respectively, among 149 children who had been newly diagnosed with the CD [32].

All subjects used in the study were regularly followed up at the outpatient clinic; whereby, only the ones who presented normal anti-tTG antibodies at the last visit were considered. Moreover, the study collected data on the weight, height and BMIat diagnosis and after at least 12 months on a GFD [32]. The results by Valletta et al. indicated that only three per cent of the children were considered

"obese"; even after a GFD, the proportion of the obese patients remained unchanged [33]. The figure below displays the correlation between CD and obesity.

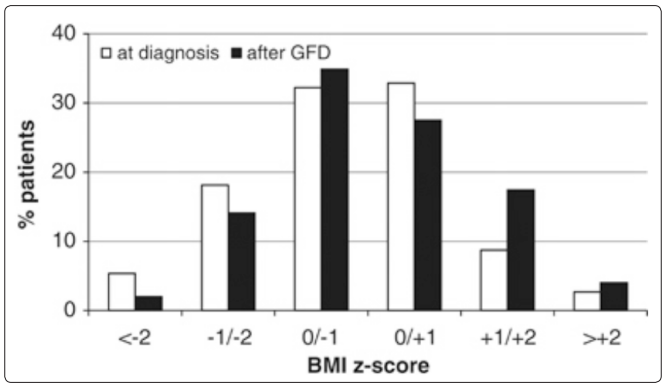

Figure 2: The Distribution of BMI z-score at diagnosis of celiac disease and after GFD (Valletta et al., 2010)

As seen in Figure 2, Valletta et al. found that upon initiating a GFD on the children diagnosed with CD, there was a significant increase in the BMI z-score with the overweight children almost doubling in percentage. Thus, Valletta et al. identified the need for nutritional follow-up with children upon diagnosis of CD [32]. However, another retrospective study conducted by Venkatasubramani et al. indicated that approximately five per cent of the patients in their study had a BMI greater than the 95th percentile from the 143 subjects diagnosed with CD [22].

In a 2011 report from Reilly et al., 142 children with newly diagnosed CD between the years 2000 and 2008 were studied. In this report, it was indicated that 19 percent of the subjects used in the study had high BMIs at diagnosis, with 6 percent considered as "obese" and 12.6 per cent as "overweight". With the introduction of a GFD, Reilly et al. indicated that 75 percent of the patients with high BMIs at diagnosis stage had decreased and the patients with normal BMI at diagnosis had significantly increased after the introduction of a GFD; resulting in 13 percent being "overweight" [34,35]. At the beginning of the study, Reilly et al. established that the initial symptom, among 28 per cent of overweight CD patients, included abdominal pain [34].

They, too, concluded and that abdominal pain was the most common symptom of CD presentation among the overweight patients, which was also discovered in a 2010 study by Venkatasubramani et al. [22,35]. The diagnoses in these two studies, where patients with CD were identified on the basis of screening tests and not the symptoms, could result in an increased probability of proper diagnosis of CD among obese and overweight persons. Likewise, Brambilla et al. reported to have compared 150 children with CD on a GFD against 288 children who were "healthy gender-and-age matched" [36]. They conducted a retrospective study to evaluate the changes in the BMI from CD at diagnosis to the last clinical evaluation conducted on the children with CD.

In the study, Brambilla et al. established that the median BMI of the CD patients was significantly lower than the other 288 healthy children. Notably, the children with CD were found to be less frequently overweight, however, the obese children were 23.3 per cent against the 12 percent of overweight children compared to the controls [36]. Importantly, the introduction of a GFD indicated a significant decrease in the number of underweight subjects, while the number of overweight patients slightly increased compared to the controlled group [36].

Similarly, a cross-sectional study by Norsa et al. had enrolled 114 children, diagnosed with CD, in a serologic remission; specifically, the children used were on a GFD for at least one year [37]. Notably, the anthropometric measurements performed at diagnosis concluded that 8.8 per cent were overweight and 5.3 percent were obese [37]. However, after gluten-withdrawal, Norsa et al. indicated that the prevalence of overweight and obesity increased to 11.4 percent and 8 per cent, respectively [37].

Lastly, a critical report that presented the analyzed prevalence of obesity among CD patients, specifically in pediatrics, is by Venkatasubramani et al. [22]. In this report, the authors analyzed the prevalence of obesity among patients for a 17-yearperiod at a hospital. The results indicated that 5 per cent of the subjects with CD were obese, with the measured BMI at >95th percentile [22]. Notably, the BMI reduced in 57 per cent of the subjects upon adherence of a GFD. However, this study had several limitations, as they only used a small group of children to conduct a long-term follow-up to provide an accurate prevalence and the possible outcome of obesity and CD.

Nevertheless, the authors concluded that, "obesity is more common among children with celiac disease than previously recognized" [22]. Therefore, it is important to note that the treatment of CD among obese children could potentially reduce the BMI [22].

Relationship between CD, obesity and liver disease

In the review of the pathogenesis of CD it is understood that the disease has typically been associated with malab sorption and weight loss. Consequently, clinicians may sometimes consider diagnosis of CD among overweight and/or obese patients, but this subgroup is most often overlooked [38]. Some studies have indicated that those who suffer from CD can often fail to display 'classic' symptoms; thus, can very well be obese, rather than underweight, at the time of presentation [30,39]. Overall, there are several health issues that have been associated with obesity and CD, one of which being non-alcoholic fatty liver disease [40,41]. Several studies have drawn the conclusion that liver abnormalities are very much associated with CD, however, more research is being focused on those with atypical presentations of CD, such as overweight, and NAFLD, specifically [42,43]. Although this area has been thoroughly researched, it still remains unclear as to whether a fatty liver is an effect, a cause or merely an connection with CD [44].

Further studies have suggested that NAFLD may be related with diet, as studies have discovered that some individuals experience their liver damage being revere dafter strict adherence to a GFD, however, more research in this particular area is needed [45,46].

An article from Tucker et al. also reported an important relationship between CD and obesity at presentation [15]. In this report, 240 patients registered with CD at the Worcester and Redditch hospital; the overall population, spread between two hospitals, indicated that the mean BMI was 25.07 and the median 23.6. The researchers analysed the patients and established that 44 per cent of which had a BMI in the obese range, while only three percent were considered

underweight, with BMI of 18.5 or below [15]. In the early group, the BMI mean was 25, while in the late group the BMI was at 25.4. The analysis of the patients, who had BMIs of 25 or over, indicated that the patients rose in risks of obesity up on presentation of CD.

In Summary, Tucker et al. established that 44 percent of the CD patients used in the study, at first referral, were either obese or overweight [15]. Signifying the importance of early and proper diagnosis, as well as obesity not being overlooked as a very real symptom for CD. Similarly, a report from Dickey and Kearney indicated the incidences of overweight or obesity in patients at the onset of CD. The researchers reviewed BMI measurements and other pathological and clinical features from the database of 371 patients, which were diagnosed over a ten-year period and were individually seen by a gastroenterologist [30].

Notably, the researchers compared the BMI of the patients at the onset of CD and after two years of following a GFD. The mean BMI for the patients was obtained to be 24.6 kg/m^2, where only 17 patients were underweight, 48 were obese and 143 overweight [30]. Overall, the patients who were compliant with a GFD reported that 81 per cent had gained substantial weight after 2 years. Research has also been focused on investigating the causes of obesity within CD. The common 'classic' symptoms, such as abdominal pain, weight loss, low BMI and Frequent diarrhoea have been considered to be indicative of the possibility of CD at diagnosis [38,47,48]. However, when an obese patient, who had no outward evidence of classic malnourishment, presented at the doctor, it would be difficult to establish CD based solely on the clinical symptoms alone [38].

Although obesity has not previously been linked with CD, new and small sub group of overweight and obese individuals are presenting with more atypical symptoms of CD and because of that, are being over looked. Further, newly identified cases of CD patients have been established to have significant amount of weight gain, especially upon starting a GFD [49,50]. However, this is the same diet that has been shown to reverse liver damage among those with CD [42,44,45].

A study by Capriati et al. 2016 on the rare presentation of obesity and CD revealed important aspects on the two conditions as the authors conducted a longitudinal retrospective study, and also reviewed the charts of the patients who were consecutively diagnosed with CD [51]. Also, the prospective study by Capriati et al. evaluated the prevalence of being overweight among CD populations; where the changes in the BMI as a measure of nutritional status change was used. The researchers measured the BMIto define the nutritional status of children; where the status was classified as underweight, overweight, and obese [51].

A total of 440 subjects were studied and the results indicated that, at diagnosis, 7.8 percent of the patients were overweight, however, the proportion increased to 9.8 percent at the end of the study. Overall, Capriati et al. verified that obesity is a rare, but prominent symptom of CD [51]. Similarly, there have been various survey reports which have indicated obesity to be present at the onset or diagnosis of CD [7,22,52]. Further, the abovementioned case reports on the prevalence of obesity among CD patients range from 8.8 per cent to 20.8 percent for the overweight patients, while among the obese patients the range is between zeros to six per cent [35-37].

However, the introduction of a GFD presented a situation which seems to increase obesity from zero to a gripping 8.8 percent [33,35]. Importantly, the study from Venkatasubramani et al. conducted fundamental research on the presentation of CD and obesity among children. The authors found that five per cent of the 143 subjects used in the study were considered obese, with BMIs in the 95th percentile [22].

Further, the 'classic' CD symptoms, such as "failure to thrive" and malab sorption during infancy and school age, has led to most physicians considering CD among the differential diagnosis of such children but not among the ones who are actually struggling with obesity [22]. Overall, the reports tend to confirm that both non-coeliac gluten sensitivity and CD are able to generate systemic inflammation and as well as malnutrition. Therefore, the combination of those consequences may result in long-term effects, such as obesity, as well as liver damage [53].

Heredity of CD and obesity

There have been numerous reports that have indicated a relationship between CD and obesity in the context of heredity. Notably, the diagnosis of CD and obesity among children has, for many years, adopted a familiar approach based on the 'classic' signs and symptoms [54,55]. Although the study from McCrea may be out of date in several ways, he derecognize that the genetic a etiology of CD indicated an increased incidence among people whose relatives have been diagnosed with the disease [56]. The author maintained that there was a strong possibility that genetic components in CD form the basis for the genetic susceptibility of the multifactorial inheritance of the disease, which recent studies and medical procedures have confirmed [56,57].

Overall, the study by McCrae provided an in depth, comprehensive indication of the familial incidence of CD based on the genetic conditions that were established to be 44 per cent [56]. Moreover, it was important noting that the findings in the research were consistent with the requirement that the susceptibility to the disease is in herited but just as a graded character [56].

Comparably, the review of other reports indicated the possibility of genetics playing a critical role in the development of both obesity and CD. In a study by van Heel et al, it was indicated that CD has a strong genetic component, which is higher compared to other common complex diseases among children and adults [55]. In this study, it was identified that there must be an HLA-DQ2 variant, which is required to cause the dietary antigens to the T cells, in order for CD to occur [55,58].

However, other research has stated that a significant number of individuals with theHLA-DQ2 and HLA-DQ8 genes will not actually develop the disorder and, likewise, not everyone with CD will be found to carry these specific genes [8]. Evidently more research and exploration needs to be done in this area of heredity and genetics.

Nevertheless, Non-HLA genetic factors were also established to play a significant role in the development of CD, where such genetic factors simply increase the hereditary risk of developing CD by up to 31 per cent [57,59-61].

Other studies that have investigated the links between genetics to both obesity and CD have indicated a possible connection between the two conditions. According to Zhernakova & Wijmenga, the

hereditary factors that have been focused on were the regions of chromosomes 5 and 19 [62]. Further, van Heel et al. (2005) identified that the inherited variants that were found in the tightly clustered chromosome labeled "2q CD28-CTLA4-ICOS" are the ones linked to CD. Katzmarzyk et al. managed to accurately measure the heritability of obesity in terms of the waist circumference and the regional and total fat distributions amongst various populations [63]. Similarly, S O'Rahilly & Farooqi, indicated that there are genes which possibly carry the obesity trait [64]. From the papers that have been reviewed, it is clear that CD is an inherited condition, as are many of the obesity cases. The two conditions are more phenotypically and genetically heterogeneous; hence, they are more complex than previously considered. Genetics play an important function in the energetic imbalance that may lead to fat accumulation in cases of obesity, and in CD, the gluten intolerance may as well be associated with genetic factors as proven by some authors [55,65]. Thus, the demonstration of the genetic background associated with obesity and CD is particularly important in determining the correlation between the two health conditions.

Pathophysiological findings for obesity and CD

A study conducted by Stein & Schuppan (2014) on new pathophysiological findings in CD and their implications for therapy indicated very important information that provides the basis for a correlation between CD and obesity [27]. In their study, Stein & Schuppan (2014) indicated that CD is becoming one of the most common diseases across the world, with the main causal agents involving the combination of environmental and genetic factors [27]. Although the environmental factor is most often and notably considered as gluten, the individual's intestinal health and microbial ecology may very well be a critical element, alongside gluten, for causal actors of CD [8].

According to a study by Murray, the pathophysiology of CD involves three processes, which culminate in the damage of the intestinal mucosa [66]. Those processes include environmental, genetic predisposition, and immunologically-based inflammation [66]. Leavers et al. and Liu et al. also established that the disease is associated with the "HLA DQ2 and DQ8 genotypes as the major pathophysiological determinants" [65]. Moreover, the study determined that infants with the specific HLA haplotype DR3-DQ2, are at a greater risk for developing CD. The HLA phenotypes (HLA-DQ) have been established to be associated with the prevalence of obesity particularly the genetic risk for two to four year olds [67]. Hence, there is a significant point of correlation on how the pathophysiology of CD and that of obesity, in the context of genetics, can be used as evidence of the two conditions existing in an individual at the same time or even passed to the next generation.

Analysis of the reports and methodology used in establishing a relationship between CD and obesity

As mentioned in the critical review of the methodology that was used in the studies summarized above, it is important to note that criterion used to define "obesity" or" overweight" in individuals is the BMI and that this tool is widely used by medical, fitness and nutrition professionals to classify an individual as "obese", "overweight", "underweight", or "normal weight" [68]. Moreover, health professionals consider the BMI as an expression of the weight of an individual adjusted to stature, which is also an index of adiposity [2,69]. Therefore, it has been strongly correlated with body fat, however, less correlated with stature.

The advantages of using the BMI as those co-relational studies include, simplicity in calculating the body mass and its large-scale studies that can assess the risks of the disease [10,70,71]. Moreover, BMI is a universal tool that accurately and systematically classifies weight due to its limitations as a single measure.

Despite the numerous advantages of using BMI in classifying an individual's weight, it has many limitations, as well as specific guidelines to its use. The internationally accepted age-and-sex standardized threshold values of BMI for the nutritional status in adults should be in accordance with the WHO [68]. Further, the curves of the weight and height of children vary with growth, especially following their development during puberty, therefore, it is required that references to various age groups such as the distribution of the percentiles with the cut-off points are necessary for every study [30]. Moreover, it is important to use various percentile tables based on the data from the reference populations that have different anthropometric characteristics.

Overall, considering the guidelines in using the BMI confirms that the studies conducted above have a discrete methodological heterogeneity. However, based on the calculations of BMI, the researchers employed various categorizations indifferent case series, which include the BMI z-score, BMI percentile, and the IOTF cut-off point. Moreover, the studies differed from the geographically diverse populations where only Brambilla et al. and Aurangzeb et al. compared the case population with a control population. Otherwise, the abovementioned studies provided a comprehensive report on how CD relates to the obesity in the context of the BMI and population variations [36,52].

Points for Nutritional Intervention

Use of human support for interventions

The primary concern in nutritional interventions is to resolve and improve the nutritional diagnosis through the provision or delivery of the food component of as pecific diet to the patient [72]. Notably, in the treatment of CD, there are various nutritional considerations that should be taken into account. Accordingly, as gluten is the main culprit for CD patients, it is important for this substance in particular to be promptly removed upon diagnosis, thus, the recommendation for a strict GFD is imperative [73-76].

It is the responsibility of the patient to avoid any and all beverage and food items, along with medications and supplements that contain any gluten, which implies that a GFD outline should be given to the patient alongside significant patient education, follow-up, and motivation [75,77]. Overall, in depth medical and nutritional intervention has been established as the only accepted and viable treatment for CD [78]. Conflictingly, as mentioned above, many researchers have found that although adherence to a GFD is the only universally accepted treatment for CD, it can easily create more problems with unwanted and unnecessary weight gain and obesity for the CD community.

Several diets have been associated with weight-loss however, not many have successful long-term weight stability. The Paleo Diet is focused around the concept of eating "wild animal-source foods (lean meats, internal organs, bone marrow, but no dairy) and uncultivated plant-source foods (mostly fruits, non-grain, vegetables, nuts, but no legumes)" [79].

The Ketogenic Diet has also shown success with weight-loss, as well as long-term weight stability. This diet is centered around low carbohydrate, high fat and moderate protein intake, which is another variation of the standard GFD, however, much more focused on keeping carbohydrate intake down due to its ability to stall the fat burning effect of ketosis [80]. The AIP diet has been widely used by the Autoimmune Disease community. This restrictive diet is centered on healing and repairing the gut by removing gut irritants [81]. This diet is highly anti-inflammatory and therefore can cause weight-loss, even if simply by reducing inflammation in the gut and through houtthe body.

Table 4: The Breakdown of Different GFDs

	Standard GFD	Paleo Diet	Ketogenic Diet	AIP Diet
GF Grains (rice, quinoa, etc.)	Yes	NO	NO	NO
Dairy	Yes	NO	Yes (if not sensitive)	NO
Legumes	Yes	NO	NO	NO
Lentils	Yes	NO	NO	NO
Nuts & Seeds	Yes	Yes	Yes	NO
Nighshades (tomatoes, white potatoes, eggplants, etc.)	Yes	Yes (except white potatoes)	Yes (except white potatoes)	NO
Vegetables (carrots, sweet potatoes, greens, etc.)	Yes	Yes	Yes	Yes
Eggs (all)	Yes	Yes	Yes	NO
Meat (all)	Yes	Yes	Yes	Yes
Meat organs	Yes	Yes	Yes	Yes
Bone broth	NO	Yes	Yes	Yes
GF Alcohol	Yes	Yes	Yes (small quantities)	NO
NSAIDs	Yes	NO	Yes	NO
Pre & Probiotics	NO	Yes	Yes	Yes
GF starches (tapioca, arrowroot, etc.)	Yes	Yes	Yes (small quantities)	NO
FODMAPs	Yes	Yes	Yes (if not sensitive)	NO
Fruit	Yes	Yes	Yes (small quantities)	NO
Refined sugar	Yes	NO	NO	NO
Unrefined sugars (maple syrup, honey, etc.)	Yes	Yes	Yes (small quantities)	NO
Oils (EVOO, Avocado)	Yes	Yes	Yes	Yes
Seed oils (flax, almond, etc.)	Yes	Yes	Yes	NO
Yeast	Yes	Yes	Yes	NO

The above table demonstrates the difficulties some might have with the Standard GFD, which is prescribed to most at the diagnosis of CD. The Standard GFD does not take low-carbohydrate, high-fat, high-protein, weight-loss, food sensitivities (beyond gluten) and gut health into consideration, as it is only meant to cut out gluten. Therefore, it is recommended that each individual diagnosed with CD should seek specific, individualized nutritional advice, as well as gather more information on the abovementioned diet variations to the Standard GFD. The aforementioned diets are considered to be extremely healing and repairing to the gut, as well as Furthermore, from the abovementioned reviews, there are many important aspects of obesity that have been considered in the intervention of the condition notably, obesity can result from genetic factors, specifically where one or both of the individuals parents have the condition [82]. However, there has been data that suggests that simply overeating can lead weight gain through the disequilibrium of calories in vs. calories out [83].

Mainly, researchers have gathered that a diet rich in carbohydrates, alongside physical inactivity, are key points that correlated with weight gain, possibly leading to obesity [83,84]. One of the nutritional intervention strategies that continue to be extensively studied and put in place is the high-protein diet [85]. Some studies have found that adhering to a this diet in particular can significantly reduce obesity in both children and adults [84].

Withdrawal of a GFD and the possible effects on obese CD patients

Previous studies have established that obesity may develop in a CD patient even after the introduction of a GFD, possibly due to inflammation, as well as increased caloric consumption and high GI intake [52,86-88]. Some of these studies conducted surveys on children where the normalization of the BMI in both overweight and underweight patients on a GFD reported varied aspects. Notably, Aurangzeb et al., Barera et al. and Valletta et al. all conducted surveys on the withdrawal effects of gluten among CD patients [32,52,89]. In the context of CD healings, the mucosal lining is recovered from gluten withdrawal; hence, there is the recovery of the energy balance

[10]. Several studies reported similar elements for the nutritional intervention of CD and obesity, whereby, the main aspect is that the restoration of the absorptive functions of the entire bowel can potentially establish a psychological redistribution of the absorptive nature in the bowel mucosa [10, 89]. Otherwise, it still remains a concern for the authors whether the withdrawal of gluten can result in the development of obesity among CD patients. In Summary, the reviewed journals indicate different levels of evidence on why there is such variability in trends of CD patients upon introduction of a GFD. Nevertheless, there was clarification on why some patients develop obesity after the introduction of a GFD. Notably, the changes in the nutritional behavior of an individual can induce the development of obesity, which may be shared by CD patients.

Mandatory nutritional follow-up after diagnosis in the case of CD and obesity

There are several reports that have shown a possible link between initiation of a GFD and weight gain for patients with CD in the context of nutritional intervention. From the study conducted by Valletta et al. (2010), it was indicated that, from year to year, that there have been significant changes in the presentation of CD, including 'classic' signs and symptoms becoming less prevalent. In the same context, some reports indicated that obesity and CD can effectively coexist during childhood and adolescent stages [30]. Notably, Vallettaet al. reviewed 149 clinical records of children with CD, specifically considering the BMI, height, and weight of the children at diagnosis and after 12 months of adherence to a GFD [33]. From the review, 11 per cent of the CD patients were considered normal to overweight, while three per cent were obese at the initial presentation [33]. The authors indicated a significant increase in the BMI z-score after the introduction of a GFD, including the number of subjects, which was found to double at 22 percent. Overall, Valletta et al. established that these results indicated the need for careful follow-up, in terms of the nutritional status upon diagnosis with CD to address cases of obesity or overweight at presentation. Analysis of the report by Valletta et al., found that there were some critical aspects of the nutritional intervention for CD and obesity that the authors have put forward. The use of the humans as the study subjects provided a clear understanding of the possible increase in weight among children and adults upon presentation of CD [33].

The results reported by Valletta et al. have been consistent with the increasing awareness about a possible link between CD and obesity [32]. Specifically, the results indicated that malnutrition, which is a symptom used by several healthcare providers, is no longer a reliable diagnostic feature of CD in either children or adults [33]. Overall, it is evident that studies suggest that a strict GFD may increases the risk of obesity, which has also led to concerns being raised about hyper-caloric content as well as the nutritional imbalance of commercial GFDs. Therefore, it is justifiable as to why the authors call for a nutritional follow-up for patients upon introduction of a GFD, due to the possible development of obesity.

Discussion

Implications of the research

The research conducted had the primary focus of establishing a relationship between CD and obesity. Consequently, the journal articles that were reviewed, mainly obtained from the PubMed, Science Direct, and the European Journal of Nutrition, gave various results concerning the mechanism review of obesity and CD. Numerous reports reviewed indicated that obesity and CD have been linked; however, it was important to establish that most studies based their conceptual and theoretical frameworks on BMI as the reference point at the first diagnosis of CD. The use of BMI was supported by various studies; among them include Cheng et al, Dickey et al. , Dickson et al., Kabbani et al. Singh et al. [12,18,30,91,92].

The main findings from the studies based on BMI were that, in the past, the majority of dieticians, nutritionists and physicians did not associate CD with being overweight or obese. However, with the rising numbers of obese populations being diagnosed with CD, the current diagnostic skill requires a comprehensive analysis of the possible presence of obesity and CD in an individual. Notably, the study conducted by Kabbani et al. (2012) established that weight-loss might begin once the CD patient, whom is also obese, starts a GFD, with 4.4 percent of the study subjects being obese. Moreover, the current diagnosis of CD does not fully relies on the presentation of the 'classic' symptoms. Otherwise, it is important to appreciate the steps that the researchers have made towards advancements in more precise and time-sensitive diagnosis of CD, whether in an obese or underweight patient, to not only use the signs and symptoms but also to use the method that considers obesity as a symptomatic problem. Therefore, it is recommended that further studies and research be conducted in order to gain a more comprehensive outlook on the specific presentation of obesity in CD. Through actively using RCTs, cohort and controlled studies, such studies could prove to be highly beneficial in establishing a critical and more concrete bond between CD and obesity, so that diagnosis and intervention strategies can be accurately administered.

Further, the results obtained concerning the pathophysiological aspects of the two conditions were important in identifying some possible points of connection; mainly, genetics play a critical role towards the development and prevalence of both obesity and CD. The unifying genotypes were established to be HLA and the non-HLA, which are the main factors that increase the inheritability of both obesity and CD. However, the results obtained may be subject to criticism simply based on sample size. The use of small sample quantities not only indicates weak effect size of the role of the genetic factors on the development of CD and obesity but may also make the studies unreliable [93].

Ioannidis also indicated that the research findings are more likely to be true particularly where large sample sizes are used, otherwise, the results obtained using the small quantities of sample sizes may need further studies using a larger sample size so as to ascertain a better understanding about the effects of genetics on CD and obesity [93].Overall, the availability of several studies indicating a correlation between obesity and CD was indicative of a positive step towards improvements for the increasing incidences of the two conditions [12,51].

The health implications for CD and obesity

The obtained results from the research and information gathered for this review, in the context of both mechanism and intervention strategies for CD and obesity, are particularly important for the enhancement of public health awareness, including diagnosis and management of both CD and obesity. The future of health care practice is bound to bring a greater understanding of why CD covers such a wide spectrum, including its more recent and significant correlation with obesity. The use of more reliable standardized and serological tests to diagnose the two conditions indicates a

replacement for the increased need of biopsies in the diagnosis of CD. Further, the increased rate of the disease detection and its eminent link with obesity improves the experience of the clinicians or diagnosing physicians, as well as the dietician or nutritionist that is treating the condition(s). These steps could lead to a better awareness and understanding of CD and obesity and aid in improving the most important intervention; diet [67].

Moreover, Eid et al. identified the need for improved diagnostic measures to help effective treatment of the conditions, since he had identified a trend of under diagnosis, specifically in the USA [94]. Therefore, Eid et al. supported the possible implication of the review of correlation for CD and obesity to act as an agent for public awareness and health care providers to effectively diagnose and treat the conditions [94].

Respectively, it would be of great benefit for more research within the 'natural prescription' field for more options and alternative approaches to gut and intestinal healing and recovery for CD [1,9,94,95].

Studies within this field have found great success with complementary lifestyle, dietary and supplemental modifications in order to properly support and heal the immune system and gut [1]. The recommendations of stress relief, adequate rest and proper exercise, alongside daily supplementation of digestive enzymes, probiotics, EFAs and multivitamins has been has been recommended to several CD patients, in addition to a healthy, nutritionist-monitored GFD [1,8,9,95]. Additionally, further research into different types of GFDs and their benefits to those with CD would be recommended. Due to the different types of gluten-free and grain free alternatives, such as buckwheat, millet, cassava, tapioca and rice, it would be highly beneficial for more information to be available on which type of GFD would deliver the best results; weight-loss, gut healing, liver-healing etc. Greater education and nutritional guidance is required for individuals to make healthier food choices whilst still adhering to a strict GFD, specifically for their individual and personal needs.

Although these suggestions and recommendations may seem obvious, if not common sense, many individuals struggling with autoimmune conditions, like CD, have not seen immediate or lasting results from diet alterations alone. Complementary lifestyle and supplementation support offer a better chance at sustained healing for the gut, immune system, as well as neurologically and psychologically [8,9]. Otherwise, it would be important for health care providers to also consider the various clinical identifications of CD and obesity mechanisms among populations and choose a potential intervention strategy for the conditions. Moreover, it is important for physicians, nutritionists and dieticians to consider the stratification of the populations and how such aspects may influence personalized interventions for CD and obesity patients.

Recommendations for primary research

Future primary studies may want to consider the following gaps in knowledge:

- Why some CD patients on a GFD become obese
- Conduct experimental therapies for CD in a randomized controlled clinical trial
- Primary research on the mechanisms of CD based on animal studies developed for specific cohort of individuals from both developed and developing countries
- Investigate a correlation between CD and ulcers

Limitations of the research to date and gaps that exist

The limitations of the present review were severely limited research concerning nutritional interventions for CD and how it links to obesity in the same context, as well as research regarding in depth information on what people actually eat whilst adhering to a GFD.

Only a few studies could justify the reliability and accuracy concerning the correlation between the nutritional intervention between CD and obesity.

Conclusion

The primary focus of this review was to establish a possible relationship between CD and obesity. This review outlined the common notions about the disease, whereby; vast medical and nutritional opinion has previously linked CD to weight loss and the inability to gain weight, as many CD patients have typically been underweight. This implied that many doctors fail to check for CD whenever overweight or obese patients present 'non-classic' or atypical symptoms of CD. However, with various technologies for disease diagnosis being incorporated in current research, there is an indication of possible association between obesity and CD. Further, numerous studies, research and trials are continually working on discovering more information regarding the two conditions in terms of presentation, diagnosis and intervention. Generally, the review of CD and obesity indicated very important aspects of the conditions, particularly among the children. Notably, several medical articles, reports and studies presented CD as an extreme form of gluten intolerance in the form of an autoimmune disease [10,35,90,96,98].

Notably, various authors indicated that CD could be diagnosed at any point in life; however, the individuals who are at a higher risk are the ones with a family history. Still, the only concrete, medically accepted, solution to managing this condition is through strict adherence to a GFD [99]. Overall, the relationship concerning obesity and CD was established to exist on two different levels: the mechanism and nutritional interventions. In terms of the mechanism of CD and obesity, there have been several reports that have indicated a link between the two conditions through pathogenetic and pathophysiological links. It was important noting the three processes that influence the occurrence and development of CD and obesity amongst different populations; genetic predisposition, environmental factors, and the immunological intolerance of the environmental factors [100].

The studies indicated that gluten is the primary environmental factor that predisposes an individual to be intolerant to foods containing the protein; thus, develops an immunological response associated with the inflammation of the mucosal lining of the intestines [5, 20,101]. The genetic factors play a role in the development and heritability of the disease; whereby the HLA-DQ2/DQ8 and the non-HLA genomic loci predispose individuals who are closely related to developing the two conditions. Moreover, the genetic factors were established to be the largest point of association between obesity and CD.

Finally, obesity appears to be more frequent in the newly diagnosed CD patients who are diagnosed on the foundation of symptoms such as abdominal pain and on the basis of the standard procedures for screening [22,35,37,]. North American children, in particular, have begun to present 'non-classic' and atypical symptoms and are

considerably more overweight, if not obese, at the time of diagnosis [35]. Finally, after evaluating all of the information gathered, it is worth reviewing the possible importance of introducing a GFD if slight gluten-sensitivity is present or in the familial history, rather than once a patient is diagnosed with CD [102,103]. Also, lending more resources to natural and complementary approaches to the management of the condition, as well as healing, could prove to be incredibly valuable [104-127].

Dissemination

The following Journals are listed for potential publications in order of preference:

1. **Journal of Nutritional Disorders & Therapy:** this is a globally recognized journal with open access, which considers the overall wellbeing and infectionson digestion system and nutritional disorders such as obesity and CD.
2. **Journal of Obesity and Weight Loss Therapy:** this is preferred because it isa peer reviewed and open access periodical that publishes information based on original findings and reviews.
3. **International Journal of Digestive Diseases:** this journal publishes innovative research and comprehensive review articles specifically concerning digestive diseases, such as CD.
4. **Current Pediatric Research:** it is preferred because of its open access and acceptance of review reports, commentaries and case reports, among others.

Preface/ Acknowledgements

The presented mechanism review on the correlation of CD and obesity is part of my Masters of Science degree course in Personalized Nutrition. Having been late diagnosed (nearly twenty-eight years) and many times misdiagnosed with other conditions than CD, I believed that this review would prove to be interesting and very much needed.

Although the studies were lacking and information surrounding this topic was difficult to gather, simply due to the absence of material, I did find some very significant research. It was exciting to be able to shed some light on a topic that has not been overly researched or even highly considered.

I feel that I have learned a great deal by completing this dissertation, specifically regarding my ability to properly and professionally dissect and analyze different research, studies and trials, and gather the essential information required.

I would like to sincerely acknowledge and thank those who have made the completion of this dissertation possible; and who have helped me out along this journey.

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