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Screening for Latent or Silent Celiac Disease "Gluten-Sensitive Enteropathy" in UAE Adults Nationals

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ABSTRACT

Celiac disease is a common condition that affects all populations around the world in all ages. It was thought before that CD is a rare disease effects only the Caucasians mainly in Europe, Australia and North America, but development of new serological tests lead to increase the prevalence of the disease around the world. The main objective of this research project is to find out the prevalence of latent or silent celiac disease among UAE nationals. Total of 1200 UAE nationals agreed to participate and answer the questionnaire for the study. Subjects visited Al Ain hospital for undergoing prenuptial tests. They were screened for celiac disease using tissue transglutaminase tTG class IgA and IgG then all seropositive cases were screened for anti-endomysium antibody (EMA) IgA and IgG and total IgA. 14 (1.2%) of the 1200 subjects were seropositive for CD and none of them had been diagnosed before the study as CD patient. The prevalence of seropositive CD for females and males was remarkably different, 13/573 (2.3%) female subjects were positive while only 1/624 (0.2%) male was positive. Such high difference in prevalence between males and females is remarkable compared with many other prevalence studies which mostly reported higher prevalence among females but not to the extent of the present study. The unrecognized cases of CD which are detected through population screening endorse the concept of celiac iceberg and therefore, population screening identifies subjects who could benefit from the treatment.

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I. INTRODUCTION

I. INTRODUCTION

Celiac disease is a chronic inflammatory condition associated with morphological changes in small intestine that result in mal-absorption of different nutrients. It is characterized by an inflammatory immune response mainly to ingested wheat gluten. Varied symptoms are associated with celiac disease, including chronic diarrhea, anemia, and iron and vitamins deficiency. Intestinal biopsy is the golden standard in diagnosis, but should be aided by serological test to determine who needs the biopsy and to differentiate the disease from other causes of intestinal villi atrophy.

To our knowledge in UAE no previous published reports on the prevalence of celiac disease in the general population or in high risk group exists. The main objective of this research project is to find out the prevalence of latent or silent celiac disease among UAE nationals. The study will hopefully form the baseline for future studies targeting high risk groups for diagnosis, treatment and follow up.

I.1Small Intestine

The small intestine is the major digestive organ in the body; after digestion is completed absorption occurs within the small intestine (Marieb, 2001). The name small intestine comes from comparing its diameter to the large intestine (Ira, 2004). Since the digestion of food start in the stomach and completed in small intestine, small intestine has special factors that play major roles in providing huge absorption area (Young & Heath, 2001).

I. 1 Anatomy

The small intestine is a twisted tube extending from pyloric sphincter in the epigastria region to ileocecal valve in the right iliac region where it connects to the large intestine (Marieb, 2001). The small intestine is the longest region in the alimentary tract of about 7 m in length (Gartner & Hiatt, 2001) and the diameter is only about 2.5 cm (Marieb, 2001). It divided into three subdivision; duodenum, jejunum and ileum.

Duodenum: First part of the small intestine, the length is about 20-30 cm and extends from the pyloric sphincter (Ira, 2004). The duodenum is curve around the beginning of pancreas. It is the shortest part of the subdivision (Marieb, 2001).

Jejunum: Second part of small intestine is about 2.5m in length and extends from the duodenum to ileum (Marieb, 2001).

Ileum : Last part of small intestine and it empties in the large intestine through the ileocecal valve (Ira, 2004). It is about 3.6m in length, the jejunum and ileum coil in the central and lower part of abdominal cavity, suspended from the posterior or abdominal wall by the mesentery (Marieb, 2001).

Microscopic Anatomy

The small intestine is adapted for nutrient absorption; the length of small intestine gives a large surface area. The wall of intestine has 3 modifications to increase the absorption surface (Young & Heath, 2001).

The circular folds (valves of Kerckring) (also, plicae circulares): are large valvular flaps projecting into the lumen of the bowel: They are composed of reduplications of the mucous membrane, the two layers of the fold being bound together by submucous tissue. The

majority of the circular folds extends transversely around the cylinder of the intestine for about one-half or two-thirds of its circumference, but some form complete circles, and others have a spiral forms. The larger folds are about 8 mm in depth at their broadest part; but the greater number is of smaller size (Gartner & Hiatt, 2001). The circular folds are more developed and significant in the jejunum than elsewhere. However, they are frequently present in duodenum and ileum (Carlos & Jose, 2005). These folds force chyme to move through the lumen and slow the movement to allow for full nutrients absorption (Marieb, 2001). The second modifications in the wall of small intestine are villi.

Villi: are mucosal surface that look like finger projections, between each villus mucosa that form into crypt called Crypts of Lieberkühn (Young & Heath, 2001). Each villus contains capillary loop ending with lymphatic channel (lacteal). In these channel the digestive food is absorbed through epithelial cells into both capillary blood and lacteal (Marieb, 2001). Few smooth muscles and fibers are placed in loose connective tissue and rich in lymphoid cells (Gartner & Hiatt, 2001). Villi are large in duodenum (the most active site in absorption) and become narrow and shorter in other part of small intestine (Marieb, 2001). Villi give velvety appearance to the lining living organ (Gartner & Hiatt, 2001). The third modifications in the small intestine are microvilli.

Microvilli: are extremely small projections of plasma membrane of absorptive cells of mucosa and sometimes called brush border (Marieb, 2001). Microvilli are cylindrical projections which are approximately 1mm tall and 0.1μm in diameter (Carlos & Jose, 2005). The cell of microvilli contains core of actin microfilament with other cytoskeleton proteins (Carlos & Jose, 2005). Besides increasing absorption surface area of small

intestine, microvilli have enzymes called brush border enzymes which complete the final stage of digestion of carbohydrates and protein in small intestine (Marieb, 2001).

I.1.2 Histology of Small Intestine Wall

The mucosa of small intestine is composed from 3 layers, simple columnar epithelium, the lamina propria and the muscularis mucosae (Gartner & Hiatt, 2001).

A-Epithelium: The epithelium cell types in the small intestine include enterocytes, goblet cells, paneth cells, M or microfold cells, entero-endocrine cells, stem cell and intraepithelial lymphocytes (Young & Heath, 2001). Villi are covered by simple columnar epithelium and the intra villi space is composed from previous cells (Gartner & Hiatt, 2001).

1- Surface Absorptive cells or enterocytes cells: are tall columnar cells and the main absorptive cells (Gartner & Hiatt, 2001) enterocytes have oval nucleus in the basal half of the cell; cells are covered with homogenous layer called the stratified brush border (Carlos & Jose, 2005). The brush border is about 25μm in length and is densely packed of microvilli, each absorptive cell contain approximately 3000 microvilli which increase the area of contact between intestinal surface and nutrients (Carlos & Jose, 2005). Microvilli are covered with thick glycocalyx layer which not only protect the microvilli from auto-digestion, but also contain enzymes that cleaves dipeptides and disaccharides into their monomers (Gartner & Hiatt, 2001). The function of these cells is terminal digestion and absorption of water and nutrients, conversion of fatty acids to triglycerides to form chylmicrons and transport the bulk of absorbed nutrients to the lamina propria for distribution to the rest of the body (Gartner & Hiatt, 2001).

2- Goblet cells: These cells distribute among enterocytes and produce mucin for lubrication the intestinal content and protect epithelium (Young & Heath, 2001). Few of them found in duodenum and the number of cells increases as they reach the ileum (Carlos & Jose, 2005).

3- Paneth Cells: Exocrine cells with secretary granules in the apical cytoplasm are found in the basal portion of intestine glands (Carlos & Jose, 2005) or located deep in the crypt. These cells protect small intestine against certain bacteria through releasing lysozymes which is an antibacterial enzymes (Marieb, 2001).

4- M. Cells or Microfold cell: Specialized epithelial cells covering lymphoid follicles of payer's patches (Carlos & Jose, 2005). They endocytose antigens and transport them to the underlying lymphoid cells where immune responses to foreign antigens can be initiated. (Carlos & Jose, 2005).

5- DNES cells: These cells produce paracrine and endocrine hormones, about 1% of cells covering the villi and intravilli surface of small intestine are DNES cells (Gartner & Hiatt, 2001).

B- Lamina propria: core of villi and from loose of connective tissue which arise above the surface of small intestine, the remainder of the lamina propria extends down to the muscularis mucosa (Carlos & Jose, 2005). The lamina propria is rich in lymphoid cell to protect the intestine against microorganism. There are certain cells inside lamina propria including:

1- Crypt of Lieberkühn or intestinal crypts: its tubular intestinal gland found between mucosa of villi (Marieb, 2001). The villi of the epithelium in continuous with that of

the gland. The intestinal gland contains variety of cells such as stem cells, some absorptive cells, goblets cells and Paneth cells (Gartner & Hiatt, 2001).

2- Regenerative cells or stem cells: are located at the base of crypts, the cell provides various epithelium cells that migrate up to the villi (Marieb, 2001). These cells replace the epithelium of crypts mucosal surface and villi. The rate of cell division is high with a short cell cycle of 24 hours (Gartner & Hiatt, 2001).

3- Paneth cells, located in the bottom of crypt of Lieberkühn, produce lysozymes as antibacterial agents (Gartner & Hiatt, 2001).

C- Muscularis Mucosa: lie beneath mucosal crypts and separate mucosa from submucosa and is composed of an outer longitudinal layer and an inner circular layer (Gartner & Hiatt, 2001). The muscle fibers of the inner circular layers enter the villous and extend through its cores to the tips of the connective as far as the basement membrane (Gartner & Hiatt, 2001). The muscle fibers contract and shortening the villus several times during the digestive process (Gartner & Hiatt, 2001).

D- Duodenal gland (Brunner's) a set of elaborated mucus secreting cells found in the sub-mucosa of the duodenum only (Marieb, 2001). The glands neutralize the acidic chyme moving from the stomach by the secretion of bicarbonate rich mucosa (Marieb, 2001).

I.I.3 Physiology of Small Intestine

Onward movement of chyme contents produced by segmental and peristaltic movement, segmental movement is a gentle and propulsion of chyme in small intestine (Wilson & Ann, 1996). The rate of segmental contraction varies along small intestine; it is high in the duodenum and low at the terminal ileum (Davis et al., 2001). Chyme in segmentation moves slowly from section segmentation at high rate to another segmentation rate at lower rate, thus the chyme moves in caudal direction where the chyme moves backward and forward allowing for more mixing (Davis et al., 2001). Another movement of small intestine is peristaltic contraction progressive contraction of successive section of circular muscle; it involves only short length of intestine (Berne & Mathew, 2000). Contraction depends more on longitudinal muscle than circular muscle (Wilson & Ann, 1996). Absorption of nutrients is the main function of small intestine, the pattern of motility of small intestine reflects the absorption process. Absorption is a process in which molecules after digestion are transported through epithelial cell that lines gastrointestinal tract and then enter blood or lymph (Berne & Mathew, 2000). Small intestine secretes lot of hormones and enzymes to complete chemical digestion of nutrients; the latter is all processes that aim to change chemical state of ingested food. These changes are due to hydrolysis changes when a compound unites with water and then splits to simpler compound (Thibodeau and Patton, 1999).

Since the duodenum is connected to many digestive gland such liver, gallbladder and pancreas, all products of these glands reach the duodenum (Larsen, 2002). Mucosal lining of duodenal secrete hormone cholecystokinin CCK hormone to force concentrated bile to be released into duodenal lumen (Larsen, 2002). CCK produces the contraction of the

gallbladder to increase the secretions of pancreatic juice rich in enzyme (Ganong, 2005). Also CCK enhances the motility of small intestine and colon, the secretion of CCK increases with contact with digestive products especially fatty acid and peptides (Ganong, 2005). When the acid chyme moves to the small intestine then it mixed with bile, pancreatic juice and intestinal juice which include water, mucus, minerals salt and enzyme enterokinase (Wilson & Ann, 1996). Pancreatic juice contain enzyme that breakdown carbohydrates (α- amaylase), protein (trypsin, chymotropsin and carboxypeptidases), fat (lipases, phospholipase esterases) (Larsen, 2002). The pancreas also secretes bicarbonate which increases the pH content of duodenum to 7-8 as a favorable pH for the actions of these enzymes (Larsen, 2002). Another hormone is secreted due to presence of the chyme is somatostain a growth hormone that inhibits the secretion of another hormone gastrin which is secreted in the stomach and inhibits the secretion of hydrochloric acid in stomach (Ganong, 2005). When the chyme is in contact with enterocytes of the villi, the digestion of all nutrients is completed, carbohydrates is converted to monosaccharide, protein to amino acid, fats to fatty acid and glycerol (Wilson & Ann, 1996). Most of nutrients are absorbed in mucosal lining of duodenum, jejunum and ileum and most of the water that enter the duodenum everyday through secretion of gastric and intestinal fluid or direct ingestion (Larsen, 2002).

Each compounds of chyme have different ways for absorption to the lymph and blood. Substance moves from the lumen of the intestine into extracellular fluid by different mechanism, some molecules move by diffusion when the concentration of molecules in the gut is higher than in the body fluid (Davis et al., 2001). Other molecules which are more soluble in water and can't cross cell membrane transport by facilitated diffusion through

channels in the cell membrane (Thibodeau and Patton, 1999). Molecules present at higher concentration in the body fluid than in the intestine or at the same concentration, require energy to move them up the concentration gradient, a process known as active transport which requires hydrolysis of ATP to drive movement directly or indirectly (Pocock & Christopher, 2006). Some molecules depend on complex process for absorption such a secondary active transport that use two processes to absorb nutrients (Thibodeau and Patton, 1999).

Duodenum and upper jejunum have the highest capacity to absorb sugar compared with lower jejunum and ileum (Berne & Mathew, 2000). Glucose and galactose as an end product of sugar digestion are taken up actively across the brush border plasma membrane of epithelia (Davis et al., 2001). Glucose enters the epithelial cell through the luminal membrane by cotransporter molecules which link the inward movement of glucose with inward movement of Na down its concentration gradients (Davis et al., 2001). Na enhances the absorption of glucose and galactose because the gradient of Na provides the energy to move both sugars against their concentration gradients. Then both molecules leave the intestinal epithelial cell and diffuse into mucosal capillaries by facilitated transport (Pocock & Christopher, 2006).

Amino acid and peptides as an end product of protein digestion are transported across brush border plasma into intestinal epithelium cells, through Na dependent co-transport mechanism similar to sugar or monosaccharide's. More than 10 separate transports have been characterized for transport of amino acid (Davis et al., 2001). When amino acids enter enterocytes they cross basolateral surface through carriers mediated transport, then amino acids enter capillaries of the villus to the liver through the portal vein. Most of amino acids

are absorbed in the first part of small intestine (Pocock & Christopher, 2006). Small peptides hydrolyzed by peptidases in the cytosol of small intestine so only single amino acids appear in the portal blood (Berne & Mathew, 2000). Small peptides transport to the enterocytes by influx of hydrogen ions and once inside the intracellular compartment small peptides broken into amino acid (Pocock & Christopher, 2006).

Fatty acids, monoglycerides and cholesterol are transported by aid of lecithin and bile salt to the intestinal lumen in absorbing cells on villi (Thibodeau and Patton, 1999). Small amount of fatty acids is absorbed directly from intestinal epithelium cells into capillary blood by passive diffusion (Pocock & Christopher, 2006). Simple lipid molecules are released to pass through plasma membrane by simple diffusion, after absorption most nutrients do not pass directly to the general circulation. Lacteals conduct the fats along series of lymphatic vessels and through many lymph nodes before releasing into the venous blood (Thibodeau and Patton, 1999). Lipid release from the smooth endoplasmic reticulum by exocytosis at the basolateral membrane and then enter the lacteals of villi and leave the intestine in the lymph from where they enter into venous circulation via thoracic duct and avoid the hepatic portal vein (Pocock & Christopher, 2006).

Fluid and electrolytes that generate from ingested food and gastrointestinal secretions are absorbed actively along the small intestine. The absorption of sodium ions is coupled with transport of sugar and amino acid, many active sodium potassium pumps in the basal membrane of intestinal epithelium cell that pump sodium out of the cell to create gradients that draws sodium passively along concentration gradients set by absorption of water (Thibodeau and Patton, 1999). Chloride ions transport actively in lower ileum, bicarbonate ions transport actively into the intestinal lumen in exchange of chloride (Davis et al., 2001).

Water is absorbed in small intestine by osmosis into blood vessels responding to the gradients force by the absorption of ions and nutrients (Pocock & Christopher, 2006). Calcium has many processes of transport and absorption, calcium moves across cell membrane by carrier or by channels (Davis et al., 2001). Once calcium enters the cell it binds to protein which may involves carting calcium to the basolateral membrane and it is exported by active transport against concentration gradients (Berne and Mathew, 2000).

Immunological Activity of the Lamina Propria

Because of the large mucosal surface of gastrointestinal tract, small intestine is exposed to many invasive microorganisms (Carlos & Jose, 2005). The lamina propria is rich in lymphocytes, mast cells, plasma cells, leukocytes, fibroblast and solitary lymphoid nodes (Gartner & Hiatt, 2001). The first line of defense is secretion of immunoglobulin of the IgA class. The antigen presenting cells and dendritic cells of the lymphoid nodes transfer the antigen to the lymphocytes to initiate the immune response. Activated lymphocytes move to the mesenteric lymph node, then form germinal centers which lead to B cell to return to lamina propria, where they differentiate into plasma cells that produce immunoglobulin IgA (Gartner & Hiatt, 2001). Another protection device is intracellular tight junction that makes epithelial cell a barrier to the penetration of microorganism (Carlos & Jose, 2005).

I.2 Celiac Disease

Celiac disease has different names celiac in children, celiac sprue in adult, coeliac disease (British spelling), non tropical sprue, gluten sensitive enteropathy, idiopathic steatorrhea (Holtmeier & Caspary, 2006).

I.2.1 Brief History of Celiac Disease

Celiac disease (CD) appeared when human started cultivating crops (Wheat, rye, barley) after long years of gathering fruit and hunting animals. The Cultivation of crops began in Fertile Crescent, the wide belt of Southeast Asia, Fertile Crescent includes Turkey, Iran, Iraq, Palestine, Syria and Lebanon (Rostami et al., 2004). Then there was a major ancient migration from Fertile Crescent to other parts of world as a result of increased family size that demanded new lands. Migration was to the Mediterranean (North Africa, Greece, South Europe) Danube Valley (Central Europe and northern Europe) (Accomando & Cataldo, 2004).

The first description of clinical entity from Roman Physician Galen named Aretaeus of Cappodocia in the second century of AD (Midhagen, 2006). Dr Galen is observation was translated by Francis Adams and printed for Sydenham Society in 1856.. In 19th century Dr. Mathew Baillie published his observation about chronic diarrhea among adult, malnutrition and abdominal gases and he suggested a rice diet to improve adult health (Guandalini, 2007).

In 1888 an English Pediatric Physician Samuel Gee gave a modern description of CD, by using an identical title of Francis Adams translation of the Coeliac Affection (Ciclitira & Moodie, 2003). Dr Samuel Gee believed that diet could cure the patients; he described a

child case had improvement in his health when he ate mussels daily but he relapsed when mussels' season ended (Guandalini, 2007).

Then many articles appeared about CD in the medical literature focusing on the clinical features of disease and manipulating of food as treatment for CD. In 1924 Dr Sidney Hass described a new dietetic treatment that was named a banana diet, a successful treatment used on 8 children suffered from anorexia, later children clinically cured from CD (Guandalini, 2007). The diet excluded bread, crackers, potatoes and all cereals. His successful treatment was based on elimination of all kind of gluten (Guandalini, 2007). The banana diet lasted for many years until World War II, when Dr Dick, a Dutch pediatrician, noted improvement of celiac children patients during shortage of cereals and relapse after return of bread. Thus, with other doctors in Netherlands they documented for the first time the role of gluten in wheat and rye in CD. In 1954 Paullay reported abnormality and inflammation of the lining of small intestine seen at operations in adult celiac patients (Midhagen, 2006). In 1956 Margot Shiner developed jejunal biopsy to obtain biopsies of the lining of the upper bowel and jejunum safety and quickly from the oral route this development allowed the doctors to link between CD and damage of the proximal small intestine mucosa (Guandalini, 2007). By mid of Sixties the diagnosis of celiac was based on jejunal biopsies showing atrophy. However, medical communities argue for the diagnosis since many of lesions could be caused by different diseases then the diagnosis for CD becomes established as complete clinical remission on gluten free diet with documentation of normalization of the lesion and finally recurrent of lesions once gluten is reintroduced in the diet (Guandalini, 2007). This criterion was proposed in 1969 by European Society for Pediatric Gastroenterology (ESPGHAN) and served the world for over more than 35 years

(Mulder & Cellier, 2005). Interlaken Criteria was over looked due to the discovery of antibodies of gluten in celiac children which anti-gliadins antibodies was. In1964, Berget identified auto-antibody in the serum of celiac children the auto antibody was anti-reticulum (Guandalini, 2007). In 1990 the Interlaken Criteria were reviewed by ESPGAN and new diagnoses were published about the criteria (Mulder & Cellier, 2005). The reviewed criteria of diagnosis of CD was based on abnormal change on biopsy on child with or without signs or symptoms, clinically clear after gluten free diet associated with disappearance of circulating antibodies. Even after serology tests, diagnosis continued to depend on intestinal biopsies (Gunadalini & Gupta, 2002). After 1990, CD was known to be associated with autoimmune disease and associated with specific genes either DQ2 or DQ8 and the target auto-antigen was identified as the enzyme tissues transglutaminase (Guandalini, 2007). In 2001, criteria for diagnosis for CD adult have been defined anticipation of the 2001 United European Gastroenterology week (UEGW) in Amsterdam, the diagnosis based on villus atrophy in duodenal histology, crypt hyperplasia and intraepithelial lymphocytosis while using diet containing gluten, then normalize through gluten free diet. Serological testing for detection of antibodies before gluten free diet is used to support the diagnosis but is not essential. HLA haplotype are circumstantial (Mulder & Cellier, 2005)

I.2.2 Epidemiology

CD disease affect all ages in different countries and races. The first study of CD epidemiology in Europe was based on clinical presentation followed by internal biopsies which lead to missing many undiagnosed cases. Wide spread of highly sensitive and

specific serological tests increased the prevalence of disease and also revealed many clinical features of CD (Accomando & Cataldo, 2004). Large cohort studies in Europe and North America were done to defined the prevalence of CD, where the population have serological screening for endomysium or tissue transglutaminase then followed by intestinal biopsy for serological positive individuals, the prevalence was found up to 1% of Western population and there were approximately 7-10 undiagnosed subjects for each known CD (Holtmeier & Caspary, 2006). CD is common in Europe, Australia and North America. Some studies suggested that the prevalence of disease is about 1:150 – 1: 300 in UK and in Ireland reach 1:80 – 1:122 (Ciclitira & Moodie, 2003). The finding of screening studies in population of Italian school children is up to 1:200 which is much more than those diagnosed on clinical basis, these finding proposed analogy of Coeliac Iceberg by Catassi (Mulder & Cellier, 2005) (Figure 1.1)

Figure 1.1: Model used to illustrate that celiac disease varies with respect to presentation and severity of symptoms (Mulder & Cellier, 2005)

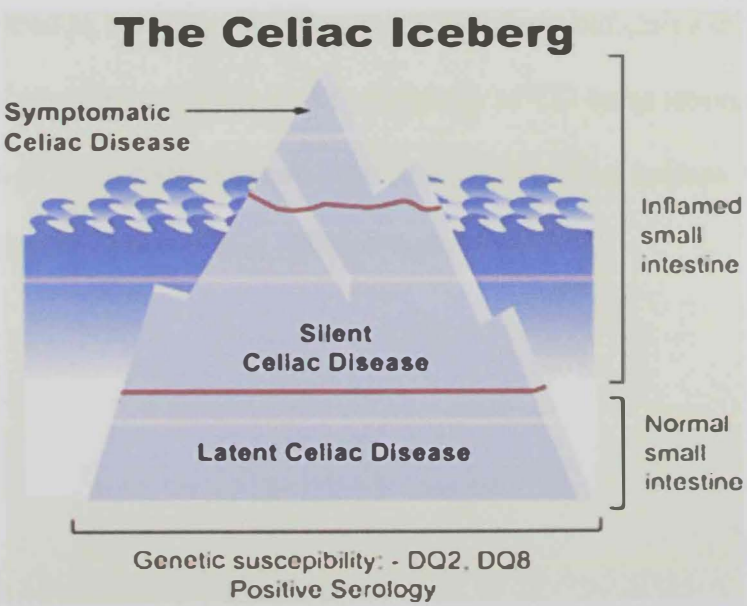


Table 1 .1: The prevalence of CD according to clinical diagnosis and screening in western countries (Guandalini & Gupta, 2002)

Area	Prevalence on clinical diagnosis	Prevalence from screening
Denmark	1:10,000	1:330
Finland	1:1000	1:130
Germany	1:2300	1:500
Italy	1:1000	1:184
Netherlands	1:4500	1:198
US	1:10,000	1:250
Sweden		1:100
Average	1:3345	1:241

More than 60% of newly diagnosed CD patients are adult; 15-20% of them are over 60 years. CD was described as a disease for European populations but, using the serological screening on nontraditional populations lead to discovery of CD cases among them. Study in US reported cases of CD among Africans American, Cuban, Dominicans and Asians from China and Philippines (Sharaf el at., 2004) (Table1. 2).

Table 1.2: Estimation of CD prevalence among different populations (Niewinski, 2008)

Population	Estimated Prevalence
General population	1 in 133
Symptomatic children	1 in 322
Symptomatic adult	1 in 105
First-degree relatives of people with CD	1 in 22
Second degree relatives of people with CD	1 in 39
Chronic disease such (type 1 diabetes)	1 in 60
African, Hispanic and Asian-American	1in 236
World wide prevalence	1in 266

In US it was thought that CD is rare disease among population, but finding of multicenter studies of CD among population with serology test was 1:133 (Accomando & Cataldo, 2004). The studies of prevalence of disease in other countries rather than Europe, Australia and North America are rare. 2 studies of prevalence of CD in Latin America one in Argentina and other in Brazil, the finding of screening 2045 blood donor in Brazil has been show 1:681 of undiagnosed CD patients (Gandolfi et al., 2000). While in Argentina screening in general population has shown an overall prevalence of 1:167 (Gomez et al., 2001). However, any study design for blood donor excluded the anemic individuals, and most of the donors are male, and many studies have found that CD is mainly in anemic individuals and female, the relation between male and female is 1:2 (Accomando & Cataldo, 2004). But some studies indicate that the effect is equal between male and female

(Ciclitira & Moodie, 2003). Since Latin American share Europe ancestry, the prevalence of CD should be higher than that in Brazil, the serological test began of both study begin with antigliadin antibody which might miss many of undiagnosed of CD (Accomando & Cataldo, 2004). The highest prevalence of CD is among population of refugee children in North Africa 5.6% of Saharawi children have positive endomysium antibodies (Catassi et al., 1999). And this high prevalence of the disease in the world might be due to genetic factors, where Saharawi people have high frequency of HLA predisposing genes (Sharaf et al., 2004). Study on healthy blood donor in Tunisia for CD prevalence based on antiendomysium antibodies was 1:355 or 0.28%. Researches could not do the duodenal biopsy due to donor confidentiality (Mankai et al., 2006). On the other part of Africa the results of CD prevalence was different: none of the 600 individuals in Central Africa has been screened for antiendomysium and tissue transglutaminase antibodies have CD despite the introduction of wheat in their diet. This result might be due to low prevalence of HLA genes among central African population (Accomando & Cataldo, 2004). Also CD has been reported in Middle East and Arab countries such Kuwait, Saudi Arabia, Lebanon and Iraq references, these reports based on diagnosis cases and its retrospective Data don't include a large number of population (Accomando & Cataldo, 2004). Furthermore, the reports are more related to high risk population of CD such as diabetes type 1 which the prevalence among them between 3-10% is higher than the population of Western Countries (Rostami et al., 2004). A large serological population screening on healthy blood donor in Iran has been revealed a high prevalence of CD reach 1:166 (Shahbazkhni et al., 2003). In North India screening of 169 families first degree relatives of CD patients by antitransgultaminase antibody have been result to 13.6% where biopsy confirmed only 8.2% (Grover et al.,

2007). The high prevalence of CD in North India is due to fact the predisposing gene type HLA between them (Catassi & Cobellis, 2007). Also wheat is stable food in north India more than Southern where they consume rice more. This explains appearance of CD in North India where it is almost near absent in other parts of India where the prevalence suggested being 1: 310 (Grover et al., 2007). The prevalence in India suggested being increase due to rising of westernization on the diet which depends on wheat (Catassi & Cobellis, 2007). CD is considered rare in East Asia (China, Japan, Korea, Malaysia... etc.) because rice is the stable diet rather than wheat (Accomando & Cataldo, 2004).

I.2.2 Environmental Factors:

Environmental factors are external triggers for celiac disease; these factors include certain proteins found in cereals. Cereal products not only trigger inflammatory response leading to destroying the small intestinal mucosa but also can lead to gastrointestinal malignancy. Bread wheat or *Triticum aestivum (*originated around 8000 years ago from hybridization of *Triticum sp.* and *T. tauschii* (Herpen et al., 2006) as one of the most important cereal have 3 basic contents that are separated by milling: the content include the outer husk or bran, the germ and the storage protein structure endosperm or white flour which constitutes 70-72% of the whole grain and it is the allergic component of the wheat (Ciclitira et al., 2005; Wieser , 2007).

Wheat can be classified according to solubility of its protein contents or the molecular weight of the proteins. On the basis of molecular weight wheat can be divided to high molecular weight (HMW) containing a large protein belong to glutenins subgroup, medium molecular weight (MMW) contain ώ-gliadins and low molecular weight (LMW) contain

most of the proteins (Ciclitira et al., 2005). There are 4 groups of protein according to their solubility in water, alcohol and salt solution (Wieser, 2007). These proteins groups include albumin soluble water, globulins soluble in salt solution, gliadins soluble in alcohol solution and glutenins insoluble in water, saline or alcohol (Ciccocioppo et al., 2005). Gliadins and glutenins, form a gluten protein which is a storage protein found in cereal grain like wheat, rye and barley and form a network in dough (Shewry et al., 2002) And it is known since more than 50 years ago that gluten is the trigger of celiac disease and both gliadins and glutenins activate the celiac disease (Dewar et al., 2004).

Hundreds of protein components are found in gluten, these proteins which are unique in their amino acid present either as monomers or linked by inter-chain disulphide bonds as oligo and polymers (Wieser, 2007). Gluten contains 75% of protein and the rest are starch and lipid. The major type of protein is named Prolamines (Shewry et al., 2002).

Prolamines are alcohol soluble structure of cereals which have high content of proline and glutamine. Other proteins found are secalin from rye, hordein from barley can trigger celiac disease (Ciccocioppo et al., 2005) Gliadins, glutenine, hordeines and secalin have high contents of proline, which is secondary amide and cause twisting in the polypeptides (Dewar et al., 2004). These proteins prevent a complete proteolytic digestion through gastric, pancreatic and brush border enzymes in small intestine (Kagnoff, 2007). Since these enzymes are insufficient in prolyl endopeptidase activity these can cause accumulation of large peptides fragment with high contents of glutamine and proline in small intestine (Kagnoff, 2007). On the bases of N- terminal amino acid sequences gliadins are designated as α-, β, γ- and ώ-types (Ciclitira & Moodie, 2003; Ciccocioppo et al., 2005). The peptide corresponding to amino acid residues 31- 49 of A- gliadins was found to cause histological

damage in small intestine specimens (Ciclitira & Moodie, 2003). Only gliadin has been investigated in detail as trigger of celiac diseases (Ciccocioppo et al., 2005). New analytical methods applied for gliadins such as two dimensions electrophoresis or reversed phase high performance liquid chromatography (RP- HPLC) allowed the separation of gliadins fraction into more than hundred component based on analysis of partial or complete of amino acid sequence and molecular weight (Wieser, 2007). Glutamine fraction contains aggregated proteins connected together by disulphide bond, the size is ranging between 500,000 to 10 million, glutenine subunit have been divided into high molecular weight HMW subunit (MW = 67,000-88,000) and low molecular weight LMW subunits (MW= 32, 000-35,000) (Wieser, 2007). Some studies indicate that low, high molecular glutenine stimulate the disease (Koning et al., 2005). These problematic subdivisions and subgroups reflect the fact that each wheat variety expresses a large number of related proteins which make study of biochemical, toxicity and gene mapping a difficult task (Ciclitira et al., 2005).

I.2.4 Genetic Factor

There are many of evidences that link CD pathogens to genetic factors. These evidences include observation of multiple cases of CD among families (Kagnoff, 2007). Around 75% of CD within identical twin have high rate of co-ordinance of CD (Woodward, 2007) comparing to 20% in dizygotic (Clot & Babron, 2000). Family studies indicate that the risk of CD in first degree relatives being 20-30% time greater than general population (Dewar et al., 2004) and the disease occur in 10% of first degree relatives. In 1972 there was first report of relation between CD and HLA complex , the relation was discovered through a serological method (Heel et al., 2005), CD is connected to the specific major

histocompatability MHC class II alleles that maps to the HLA-DQ locus (Kagnoff, 2007). MHC is the cluster of genes that display cell associated antigen for recognition by T cell (Abbas & Lichtman, 2005). MHC is referred to as HLA complex in humans which divides into 3 classes of molecules one of them class II MHC genes that express mainly on antigen presenting cell APC such macrophage, dendritic cell and B cell where they present processed antigenic peptides to TH cell (Goldsby et al., 2003). The genetic factors of HLA complex was estimated to account for 50% of genetic load of CD (Tollefsen et al., 2006). Two alleles encode specific HLA the HLA –DQ2 and HLA- DQ8 heterodimer that confer relatively higher risk to CD are formed by β and α chain (Heel et al., 2005). β chain encoded by alleles HLA – DQβ*02 (Either HLAβ1*202 or 203) and α chain encoded by alleles HLA- DQA1*05) (Kagnoff, 2007). About 95% of CD patients carry a different of DQ2 encoded by DQA1*5/ DQB*2 and the remaining of celiac patients carry DQ8 encoded by DQA1*03/DQB1*0302 (Vader et al., 2003; Tollefsen et al., 2006). DQ2 can be encoded *cis* in same haplotype or rarely in *trans*, the monomer subunit are encoded on separate haplotype both *cis* and *trans* are different in one of amino acid which does not affect the disease risk (Heel et al., 2005). Another relation of genetic factor to the CD is autoimmune disease such type 1 diabetes mellitus, rheumatoid arthritis share CD the HLA complex (Dewar, 2004). 50% of the genetic load is referred to as the HLA complex and about 30% of health Caucasians carry the HLADQ2 (Heel et al., 2005). These finding suggest that carrying HLA complex is not sufficient to cause CD but is necessary, and there are another genetic factors participate in disease. To identify other genetic factors genome wide linkage studies have been performed in different population in Europe. These studies based on analysis of nuclear families affected by CD in different countries (Clot & Babron, 2000). In

Study performed in Dutch, two loci are identified for CD located in chromosomes 5 and 19 (Heel et al., 2005). Other candidate genes found on chromosomes 2,3,4,5,6,11, 18 and 19 (Kagnoff, 2007). Some candidate genes belong to immunity response such CTLA- 4 cytotoxic T lymphocytes (Clot & Babron, 2000). However, these genes have low risk of CD exposed comparing to expressing of DQ2 and DQ8 (Kagnoff, 2007). Some genes are identified in some population but not all; therefore, more studies are needed to identify more accurately the predisposing genetic factors for CD.

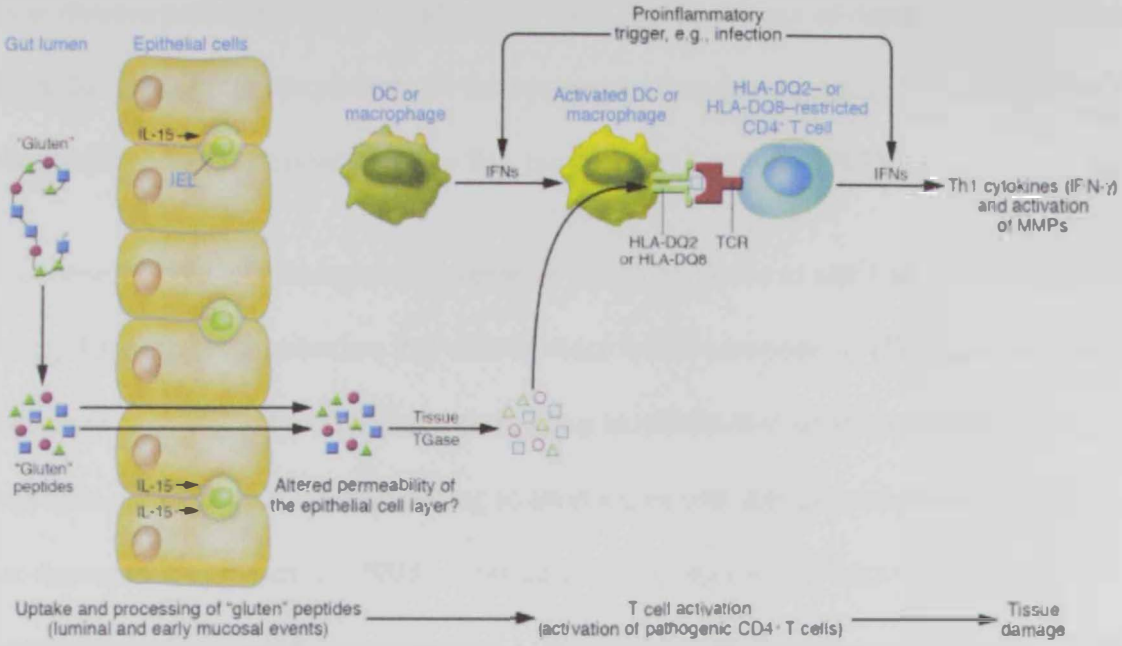
I.2.5. Immunological Factors

Gluten protein can activate innate and adaptive immunity arms of the immune system. The innate immune or the natural immunity is referred to as non specific, rapid and without memory immunity (Goldsby et al., 2003). In CD the innate cells release cytokines that regulate and coordinate many activities of the cells of the adaptive immunity (Abbas & Lichtman, 2005). Interleukin 15 (IL-15) is one of the cytokine released by many cells but mainly dendritic cells that stimulate, proliferate develop and activate of T cells (Goldsby et al., 2003). Adaptive immunity is mediated by lymphocytes and is more specific and has memory (Abbas & Lichtman, 2005). In CD the adaptive immunity mediated through T cells which bind to HLA loaded by gluten peptides. According to Kagnoff, 2007, the immuno-pathogenesis model of the T cell response in CD is divided to the 3 phases; early event located in Lumina and mucosal, activation of the pathogenic CD4 and event that lead to tissue damage.

Early event in lumina and mucosal: Gluten is digested through gastrointestinal enzymes to peptides (Koning et at., 2005). Since there is lack of prolyl endopeptidases

in gastric, pancreatic and brush border large peptides of gluten which is rich in proline and glutamine remain after initial digestion (Koning et at., 2005). In individuals with increase susceptibility to CD because of genetic, immunological or environmental event (infection with enteric virus) peptides of gluten activate series of immunological events that lead the digested peptides attached to antigen presenting cells in subepithelial region of the small intestine to many pathways; may include the uptake of peptides by dendrites cell process that cross the epithelial cell layer or facilitated by the uptake of gluten peptides to small intestine mucus by oral infection or any other infection that cause inflammation , then gluten peptides bound to HLA DQ2 or DQ8and this activates gluten specific CD4 mucosal T cell which activate T_H cytokine production, last stage of immuno-pathogenesis is releasing of cytokines such IFN-γ and others lead to continue response and change key mucosal function including intestinal permeability can also lead to activation and release of enzymes that can damage the mucosa, resulting in loss of villi structure and crypt hypertrophy (Kagnoff, 2007) (Figure1.2).

Figure 1.2: Immunological reaction against gluten



This schematic divides the pathogenesis of CD into 3 major series of events: luminal and early mucosal events; the activation of pathogenic CD4+ T cells; and the subsequent events leading to tissue damage. During the luminal and early mucosal events, key features include the ingestion of "gluten" by a genetically susceptible individual. "Gluten" is not fully digested because of its high proline content, and this gives rise to a number of large undigested "gluten" peptides. The peptides cross the epithelial barrier to the lamina propria and encounter tissue TGase and APCs that express HLA-DQ2 or HLA-DQ8 heterodimers that are ideally suited to bind proline-rich peptides containing negatively charged glutamic acid residues as a result of glutamine deamidation by tissue TGase. In a further series of events, the APCs present some of these peptides to HLA-DQ2– and HLA-DQ8–restricted populations of CD4+ T cells that become activated and release mediators that ultimately lead to tissue damage. There are still many unknowns. These include the mechanism by

which "gluten" peptides cross the epithelial cell barrier, the role of innate immunity and IELs in both the early and the late phases of CD pathogenesis, the role of IL-15 and type I IFNs in disease pathogenesis, the underlying basis for the release of tissue TGase that leads to deamidation of gluten peptides, and the sequence of, and relationship between, CD4+ T cell responses and the responses of the IEL population (Kagnoff, 2007).

CD is considered as an autoimmune disease in which response to self tissue leading to tissue damage, there are autoantibodies that able to react to self components (Delves et al., 2006). Self antigen can't easily be eliminated comparing to elimination of strange invaders, an autoantigen presence in the body leading to production of more autoantigen as a result of tissue damage (Janeway et al., 2005). Interaction of nonspecific effectors cells such as macrophages and neutrophils that respond to release of cytokines and chemokines, thus, the self destructive process is continuing (Janeway et al., 2005). Autoimmune diseases have genetic factors and tend to be found in certain families or cluster in one person; there is more chance of having autoimmune disease in both identical twins than non identical twins (Janeway et al., 2005; Delves et al., 2006). Risk of getting an autoimmune disease is associated with presence of HLA genes, the relative have high risk of the particular disease by comparing to the disease frequency among the carriers of particular HLA genes with the frequency of the disease among non carriers (Doah et al., 2008). Moreover, most of the autoimmune disease is linked strongly to MHC class II alleles. This relation between MHC and autoimmune disease relate to the fact that immune response is required. T cell and its ability to recognize particular antigen is dependent on the MHC molecule haplotypes (Janeway et al., 2005). Many autoimmune diseases are more common in females than males and this due to unknown factors (Goldsby et al., 2003). Environmental factors influence

getting autoimmune diseases, there are evidence in animals models that some kind of toxins in the environment can lead to autoimmune disease such heavy metals gold and mercury. In Animals models both of those heavy metals when administrated to genetically susceptible strains of mice lead to autoantibody production which fit with the CD model (Janeway et al., 2005).

I.2.6.Clinical Presentation

A lot of clinical presentations are associated with CD patients. The symptoms of celiac are manifested in adult at the fourth or fifth decade. On other hand, the symptoms can occur in children in early life then subside for many years then reappear again in adulthood. Some researches refer to physical or emotional stress that leads to sing and symptoms become noticeable in adulthood after existing sub clinically for years (Early,2005). Most of clinical presentations are due to intestinal features and those caused by mal-absorption of nutrients and vitamins (Holtmeier & Caspary, 2006). However, the presentations of disease depend on cases and particular practice of patients (Westerberg et al., 2006). Symptoms of CD are very broad spectrum of clinical features. Clinical presentation of CD has been divided into 4 categories, these categories include typical, non typical, silent and latent. Typical presentation refers to CD patients suffering from gastrointestinal manifestation such as diarrhea, abdominal pain, distension, weight loss, steatrohoea, constipation and indigestion (Jones et al, 2006; Westerberg et al, 2006). Non typical CD patients refer to patients who present extraintestinal symptoms such immunoglobulin IgA, nephropathy, hemosiderosis of lung (Holtmeier & Caspary, 2006). Less common manifestation include neurological condition such ataxia, dementia, and epilepsy (Early, 2005). The term silent refers to patients asymptomatic who appear healthy and lack diarrhea (Holtmeier & Caspary, 2006,

Jones et al., 2006). Moreover, many CD silent patients have minimal or no abnormalities in villous structure (Freeman et al., 2002). But the patients are positive in serology test and typical HLA predisposing (Fasano & Catassi, 2005). The term latent refers to individuals who will develop the disease later on life and they have positive serology test and HLA with no abnormalities of villous and it's unknown what trigger the symptoms for these individuals (Holtmeier & Caspary, 2006). Mode of CD presentation have been changed, study of 252 celiac patients in adult in Italy revealed that only 43% of them show classic gastrointestinal symptoms due to deficiency of nutrition's such as iron, calcium, folic and depletion of mineral and ions such as potassium, zinc and magnesium (Early, 2005). Some patients present overweigh, reflecting the obesity tendency in some individuals (Furse & Mee, 2005).

Females differ in their presentation for CD than male, symptoms present more sever, diverse and rapid symptoms at younger age (Early,2005), some studies indicate that females have high risk of suffering from miscarriage, low birth weight children (Ciclitira & Moodie, 2003) and CD might responsible of unexplained infertility (Guandalini & Gupta, 2002). The relation between severity of symptoms' and the villous atrophy are still conversional, some studies refer that the severity of symptoms is not necessarily proportional to the severity of mucosal lesion; patient might have total villous atrophy and can be asymptomatic or present with subclinical symptoms such muscle cramps and iron deficiency (Holtmeier & Caspary, 2006). While some studies refer that the severity of symptoms and mal-absorption are directly influenced by degree of enteropathy (Westerberg et al., 2006).

There are associations between CD and some disease in adult such dermatitis herpertiformis which is the most common disease for CD and effect 25% of patients (Westerberg et al.,

2006). Dermatitis herpertiformis is skin disorder associated with villous eruption on the elbows, buttocks and back, and it has been seen that conditions respond to gluten free diet (Westerberg et al., 2006). Other disorders are autoimmune thyroid disease, thyroid lymphoma, type I diabetes mellitus, autoimmune liver disease and inflammatory bowel disease (Freeman et al., 2002). The longer exposure to gluten is linked to higher incidence of autoimmune disorder (Westerberg et al., 2006). The pathogenesis of autoimmune thyroid disease and CD are not known, but it was known that all these condition sharing same HLA haplotype and are associated with encoded cytotoxic T lymphocytes associated antigen (Ch'ng et al., 2007). CD also common for individuals suffer from IgA deficiency, However, no difference for clinical presentation between them and other CD patients, but there an over presentation of silent and atypical symptoms was observed among them (Dahlbom et al., 2005) as shown in (Table1. 3).

Table 1. 3: Common signs, symptoms and associated conditions of CD (Westerberg et al., 2006).

Common Associated Conditions with CD	**Signs and Symptoms of CD in Adult**
Autoimmune Disorder Type 1 diabetes mellitus Dermatitis Down syndrome Epilepsy Immunoglobulin A deficiency Osteoporosis or other bone disease	Abdominal Pain Chronic diarrhea Infertility or recurrent spontaneous abortion Iron deficiency anemia Irritable bowel syndrome Peripheral neuropathy Weight loss Thyroid disease Turner syndrome

Patients with CD have high risk to develop bone metabolism (Jones et al., 2006). Other complications include developing esophageal cancer, melanoma and small intestine adeonocarcinoma (Westerberg et al., 2006). In general, people with CD are at modestly increase risk of malignancy and mortality compared with general population (West et al., 2004). On other hand, some studies suggest more than modest increase in mortality and malignancy among CD patients compared to the general population (West et al., 2004).

I.2.7 Diagnosis

The diagnosis for CD is usually the target of individuals who have clinical presentation or condition associated with CD; physician must consider testing the asymptomatic individuals who are in highest risk of developing the disease (Westerberg et al., 2006). The high risk group of having CD include the first relatives degree of CD patients, type I diabetes mellitus, Down syndrome, autoimmune thyroiditis , unexplained metabolic of bone disease, irritable bowel syndrome, chronic liver of unknown functional dyspepsia, unexplained fatigue and neurological disorder (Early,2005; Westerberg et al., 2006). Beside individuals with manifestation of mal-absorption of nutrients and mineral such iron, folic acid, calcium, vitamin K, D, E and unexplained weight loss (Green et al., 2005). Also females with infertility or miscarriages should be considered by physicians as a high risk group (Mulder & Cellier, 2005).

CD patients produce amount of immunoglobulin such IgA, IgG and IgM and other antibodies against reticulum, gliadins, endomysium and tissue transglutaminase, these finding lead to introduce serology tests to detect antibodies against CD (Early,2005). The serological tests are simple, not expensive and require blood serum only and it's widely available. Some studies suggest that patients with low to moderate probability of having CD can be subjected to serology screen rather than biopsy (Abdul Karim & Murray, 2003). Serology tests are helpful for high risk patient and to monitor the adherence to gluten free diet (Abdul Karim & Murray, 2003).

Anti gliadins antibody (AGA) is the first serology test that has been introduced in early 1980 for CD diagnosis. AGA detects the antibodies in serum and is widely available and not expensive (Guandalini & Gupta, 2002). The test measures two type of immunoglobulin

IgA and IgG. The most sensitive tests are based on use IgA isotype, IgG AGF have been found in 30% of controls; therefore, a positive test is of little value (Guandalini & Gupta, 2002; Green et al., 2005). The specificity is different depending on the laboratory centers some the range refer 82- 100% (Guandalini & Gupta, 2002; Early, 2005); while the sensitivity is low and it ranges between 70 –92% (Guandalini & Gupta, 2002; Early, 2005; Green et al., 2005). Because of the low sensitivity of AGA and discovering of new more accurate tests, the test is no longer used like before; the test is mainly used now to monitor response to the GFD (Abdul Karim & Murray, 2003). Another limitation for the AGA is due to the presence of the antibodies in healthy individuals and in the inflammatory bowel syndrome (Westerberg et al., 2006). There are no reference on the sensitivity and specificity of anti-reticulum antibodies test (Green et al., 2005). The Second test available for CD screening is endomysium antibodies EMA, a connective tissue protein found in the matrix of monkey and human tissue (Abdul Karim & Murray, 2003) The test is based on immunolforescence using monkey esophageal section or human umbilical cord smooth muscle as antigen source and sera from patient being tested (Guandalini & Gupta, 2002). The test has high specificity that reach up 100% in some studies, the sensitivity reach 90%. The high specificity and sensitivity lead some investigators to suggest that there is no need for biopsies with positive EMA (Freeman et al., 2002; Guandalini & Gupta, 2002; Abdul Karim & Murray, 2003; Green et al., 2005). However, the test is expensive and requires the use monkey esophagus which is endangered species or using human umbilical cord as substrate that limit the screen for the large population (Guandalini & Gupta, 2002; Green et al., 2005). Also it requires technical experience in performing the test (Abdul Karim & Murray, 2003). Besides that reason the presence of EMA correlates with degree of villus

atrophy (Mulder & Cellier, 2005). The sensitivity of the test reachs 100% when using umbilical cord and human jejunum as substrate but is less when individuals have less severe degree of small intestine villus atrophy (Abdul Karim & Murray, 2003).

The newest test for CD screening is anti-tissue transglutaminase antibodies anti-tTG. Tissue transglutaminase is intestinal enzymes release from injured cells, the enzymes link with gliadins to become a target of antibodies response the mucosal injury stop when eliminating gliadins (Early,2005). In 1997 Dieterish and colleagues identified tTG as the autoantigen of CD or for EMA (Abdul Karim & Murray, 2003). This discovery allowed to develop Enzyme Linked Immunoabsorbent Assay (ELISA) the antigen first was derived from the guinea pig liver the sensitivity for guinea pig IgA tTG antibodies was found to be 98% while specificity was found to be 94% in patient with biopsies proven CD (Guandalini & Gupta, 2002). Then the test is replaced with human tTG an antibody is better performed than guinea pig (Green et al., 2005). The test detects both immunoglobulin IgA, IgG, sensitivity of human tTG is more than 90% but the specificity is less than EMA (Green et al., 2005). The test based on ELISA and it is not costly and not time consuming compared to EMA (Guandalini & Gupta, 2002). The serology test of EMA and tTG are limited due to many factors, both tests are underestimating the prevalence of CD by 20-25% , incaution of patients with mild mucosal change in this situation patients can't express EMA or tTG and the mucosal lesion become less express (Green et al.,2005). Seronegative results have been found for smoking individual. Furthermore, most studies have been performed on high CD prevalence group, thus, the positive predictive value of test is lower than reported when the serology tests is applied in general population (Mulder & Cellier, 2005). About 2-6% of diagnostic CD individuals have IgA deficiency that occurs mainly in CD patients (Dahlbom

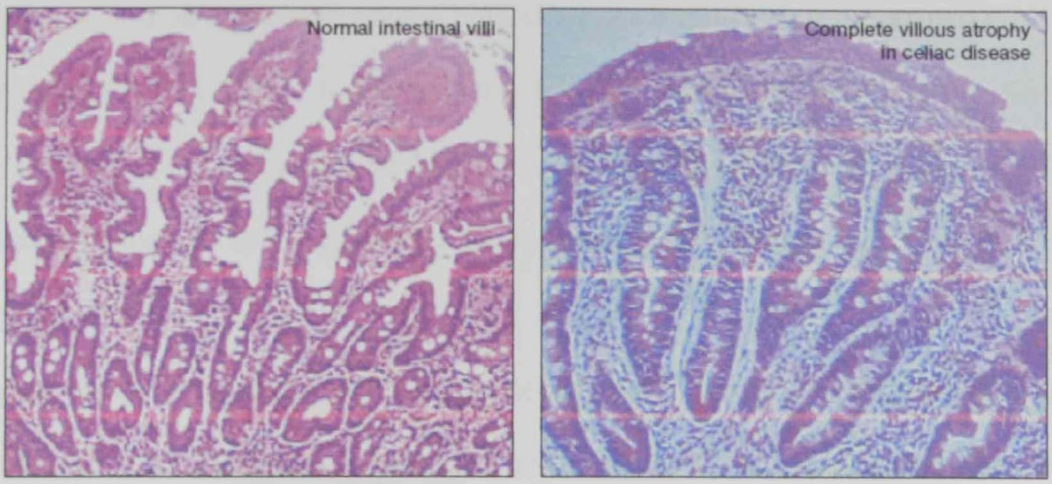
et al., 2005). Therefore, the patient lack IgA in AGA, tTG and EMA and the serology test become negative (Abdul Karim & Murray, 2003) Testing for IgG antibodies in association with total Human IgA is more reliable for IgA deficiency (Guandalini & Gupta, 2002). HLA DQ2 or HLA DQ8 alleles are found in more than 40% of population and it appears that the test for HLA typing is necessary but not sufficient by its own as there are high negative predictive values of CD (Green et al., 2005). The test is used to identify individuals at high risk to develop CD (Westerberg et al., 2006); it is good in diagnosis of first degree relatives. Moreover, the test is required when diagnosis not confirmed by other tests and the absence of DQ2 or DQ8 rule out the disease (Abdul Karim & Murray, 2003).

Biopsy of small intestine is the golden standard for confirming the diagnosis of CD and therefore, positive serology results should be confirmed by biopsies (Freeman et al., 2002; Guandalini & Gupta, 2002). The goal from biopsy is to recognize the villous atrophy in mucosal specimens (Westerberg et al., 2006). Most biopsy is performed during upper endoscopy; biopsy should be obtained from the second or third section of distal duodenum to avoid architectural changes of duodenal gland (Brunner's) (Westerberg et al., 2006). Several studies have compared duodenal biopsies with section of jejunal biopsies in the same patients and found that there is rarely any difference between the sections (Abdul Karim & Murray, 2003) Several abnormal change might be seen in intestinal biopsy, these changes include increase number of the lymphoid cellular element in the lamina propria, increase of intraepithelial lymphocytes, increase cuboidal surface of epithelial cell rather than columnar epithelial cell, hyperplasia with increase epithelial cell (Freeman et al. , 2002). In 1990 Marsh prove a spectrum on consecutive stage of mucosal abnormalities that

can be seen in CD patients. This reveal to Marsh Classification of small intestine lesion (Mulder & Cellier, 2005). The stages of classification are as follows:

Stage 0 is characterized by pre infiltration mucosa (Abdul Karim & Murray, 2003) Marsh I is characterized by lesion architecture of the mucosal look normal and the mucosal epithelium is invaded by lymphocytes and infiltration of the lamina propria (Mulder & Cellier, 2005). These changes can be seen in many diseases and not exclusive for CD (Green et al., 2005). Marsh II lesion is characterized by crypt hyperplasia and lymphatic enteritis (Mulder & Cellier, 2005). Marsh III lesion is characterized by flat lesion contain intraepithelial lymphocytosis, crypt hyperplasia and moderate to severe villous atrophy (Abdul Karim & Murray, 2003). 50- 60% of CD patients fall into this Marsh category (Green et al., 2005). March 4 is characterized by irreversible hypoplastic atrophic lesion in which malignant (lymphomatous) transformation can develop (Mulder & Cellier, 2005) or total villous atrophy (Abdul Karim & Murray, 2003). Normal biopsy never excludes an underling presence of latent DC (Green et al., 2005). Villous atrophy can be found in many diseases but positive serological tests are rarely found in those diseases as shown in figure 3 (Abdul Karim & Murray, 2003).

Figure 1.3: The different between normal intestinal villi and complete villous atrophy in CD (Early, 2005)



1.2.8 Treatment

The only treatment for CD is the strict adherence to gluten free diet (GFD) food (Freeman et al. , 2002; Early,2005; Green et al,2005), the word wheat free product is not necessarily mean gluten free because gluten found also in rye, and barley (Westerberg et al., 2006). There is no threshold below which some GFD might be tolerated, according to the Codex Alimentarius Standard which is published in 1995 that define GFD as food containing <0.3 % protein from gluten (Shepherd & Gibson, 2006). Many European and parts of USA follow the Codex standard. Food Standard Australia and New Zealand FSANZ have defined GFD as food that have no detectable gluten and not contain oats and malt (Shepherd & Gibson, 2006). The best outcome for CD patients whether follow Codex Standard or zero tolerated has not been resolved (Shepherd & Gibson, 2006). Generally no scientific data suggest what is amount of gluten that can be tolerated, thus, zero tolerance is recommended (Abdul Karim & Murray, 2003). Placing oats is still controversial some studies confirm that

oat is safe for most CD patients for period of up 6 months (Freeman et al., 2002). Nerveless, there is no grantee that oat is not contaminated with wheat during manufacture. Therefore, oats should not be permitted until clinically improvement occurs in GFD (Shepherd & Gibson, 2006). Improvement seen in the small intestine biopsy with GFD has been documented in elderly patients with intestinal lymphoma (Freeman et al., 2002). Mucosal pathology should be normalized in response to GFG within 6-12 months (Early, 2005).

Canadian Celiac Association (CCA) has made survey on 2681 of the members to evaluate the impact of GFD of their health (Zarkadas et al., 2006); 83% of respondents report feeling a lot better and recovering from many symptoms that affect their life and health (Zarkadas et al., 2006).

Upon the diagnosis of an individual as CD patients, physicians should immediately refer the patient to a dietician with expertise in CD. Qualified dietician should provide all restrictions, recommendations and guidelines for patients (Mulder & Cellier, 2005). If the patient is not responding to GFD after 6 months or longer and they may return to the symptoms such diarrhea, fatigue and weight loss, this case is named a refractory sprue; it is a severe villous atrophy which develop later to bowel lymphoma and other cancer (Early, 2005). Patient should know that following a gluten free diet is not easy. GFD is more expensive and the food not tasty than food he used to eat. Patient should understand that the diet is long life term (Westerberg et al., 2006). Strict adherence to the GFD is the only protective effect against malignancy in adult (Freeman et al., 2002). Canadian Celiac Association members identifies some difficulties related to GFD such avoiding travel and eating outside the home, finding GFD food with a good quality, avoiding restaurants and

worrying about staying in hospital (Zarkadas et al., 2006). Patients should be aware of hidden gluten product such a medication like vitamins and mineral supplements, some kind of modified processed food, starch and vegetable gum (Early, 2005). It is necessary to supply patient with nutrients supplementation of iron, folic acid, and vitamins these supplementary should be given to all elderly patients due to long duration of subclinical disease and the potential risk of multi deficiencies. Long term supplementations are not necessary once clinical improvement has been achieved (Freeman et al., 2002). Others problems of GFD that cereals serve as primary grain food in most cereal based food these include bread, cookies, cake, pastries, pasta products, wheat is used as thick binder in many soup, sauces and dressing, sea food , sausage and used as coaling on meat and fish (Zarkadas et al., 2006). There is no international regulation in the world requires food and drug companies to label products for gluten contents (Early, 2005). In 2004 Food Allergen Labeling and Consumer Protection Act; based regulation that force companies to provide a clear statement if the product contains the top 8 food allergens including wheat (Mulder & Cellier, 2005).

I. 3 Objectives

1. To find out the seroprevalence of sub-clinical and silent celiac disease among UAE adults in Al Ain.
2. To find out the prevalence of CD cases among healthy UAE nationals adults based on small bowel biopsy.
3. To advise the volunteers with confirmed CD to be aware that they are diagnosed as having Silent or latent celiac disease and should mention this to their doctors whenever the need for treatment arises in the future.

II. MATERIALS AND METHODS

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II.1 Subject and Method

II.1.1 Study Area

Al Ain is the second largest city in the Emirate of Abu Dhabi, after the capital itself; located 160 km east of the capital, and approximately 140 km southeast of Dubai.

II.1.2 Study Design

In UAE, the prevalence of CD is not known though cases; both nationals and expatriates, are diagnosed in hospitals. We hypothesized that celiac disease remains under-diagnosed because of the wide spectrum of clinical presentations that adults with celiac disease can manifest i.e. the famous saying that we see the tip of an iceberg may well apply to the disease condition in UAE. If the above is true the need to perform a prevalence study among UAE nationals to find out the prevalence of celiac disease and to raise the awareness of the medical practitioners and the general population against the disease becomes evident.

This study is a cross-sectional seroprevalence study of CD among adult UAE nationals undergoing obligatory prenuptial examination. A total number of 1200 subjects were included. All subjects were screened for both human tTG IgA and human tTG IgG. Seropositive subjects were tested for endomysium antibodies (EMA) and those positive were asked to volunteer for small bowel biopsy to confirm serological results. A questionnaire was filled for each subject including personal information and questions on the general health status in addition to basic demographical information.

II.1.3. Study Population and Blood Sampling:

Blood was obtained from UAE nationals undergoing obligatory premarital examination in Al Ain Hospital. A total of 1200 subjects were sampled including 574 females and 626 males. The age of the subjects ranged from 15- 70 years.

Blood sampling was carried out between 23rd of September 2007 to 2nd of April 2008. From each subject, 5 ml of blood was obtained in plain tube and, sera were separated on the same day by Centrifugation for 10 min at 2500 rotations per minute (rpm) and stored at -80° C until used. For each subject a questionnaire was obtained including information on name, contact address, age, gender, education status, knowledge about CD, if previously diagnosed as CD patient, any diagnosis of CD in 1st degree relatives, history of chronic diarrhea, anemia, headache, diabetes, tumor and thyroid anomaly.

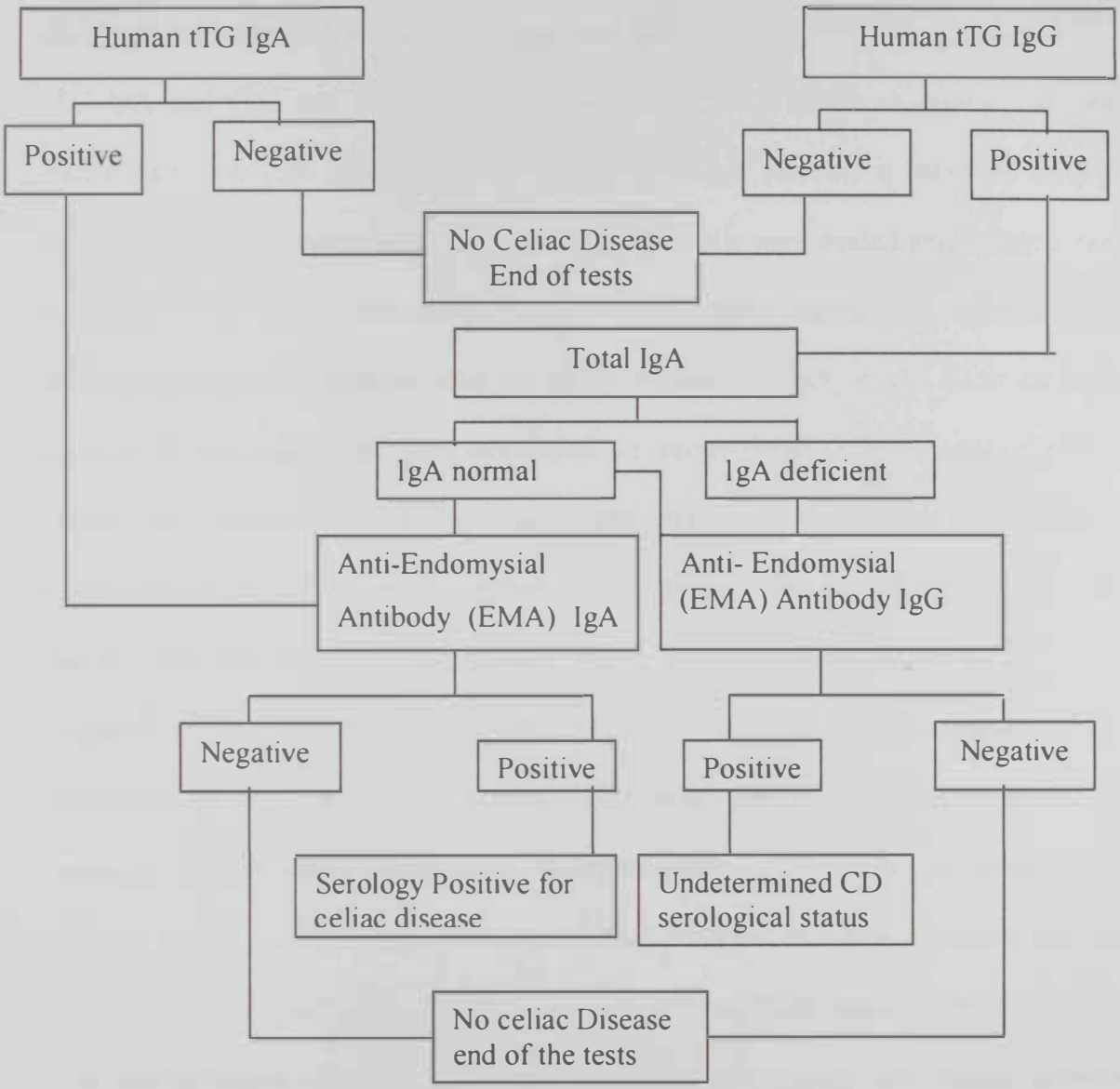
II.1.4 Ethical Aspects

Ethical clearance was obtained from the Research Review Committee at Tawam Hospital in July 2007. A written consent was signed by each subject agreeing to participate in the study after fully explaining to him/her the objectives and the expected benefits of participating in it. Healthy subjects with serologically confirmed celiac disease diagnosis were informed that they have a latent/silent celiac disease and were advised to reveal this information to their physicians if in the future they complained from any symptoms. Moreover, an overview of the disease was given to every volunteer diagnosed as having a latent/silent celiac disease in order to make him/her familiar with the different facets of the disease (see appendices).

II.1.5 Serodiagnosis Criteria:

A sample was tested for celiac disease according to the following flow chart (Fig. 2. 1)

Figure 2.1: Flow chart for CD serodiagnosis.



Finally, all serology positive subjects were asked to undergo upper gastrointestinal endoscopies. In this study the following criteria will be used to identify subjects as having confirmed CD, if biopsy showed Marsh 1, 2 or 3 type lesions with positive serology.

II. 2. Methods

II.2.1 Tissue transglutaminase tTG- IgA and IgG

tTG IgA and tTG IgG ELISA was measured using kits based on human recombinant transglutaminase (IBL Diagnosis Company, Germany). The test is based on solid phase enzyme linked immunosorbent assay (ELISA). The wells were coated with antigen; specific antibodies if present in the sample bound to the antigen coated wells were detected by secondary enzyme conjugated antibody (E-Ab) specific for IgA or IgG. After the substrate reaction the intensity of the color developed was proportional to the amount of IgA or IgG specific antibodies detected. Results can be determined directly by using the standard curve as quantitative or qualitative the optical density the positive controls to 0.21 for tTG IgA and 0.31 for tTG IgG . Each kit contains the following 6 calibrators A, B, C, D, E, F as standards and their concentrations were 0.1, 1, 3, 10, 30, 100 U/ml, receptively of IgA antibodies against transglutaminase in TBS buffer and preservative. Positive control contained IgA antibodies against tissue transglutaminase in TBS buffer and preservative and negative control in TBS buffer and preservation. Enzyme conjugate contained anti human IgA conjugated to peroxidase in buffer and preservative, TMB substrate solution contained TMB and hydrogen peroxide. Microtiter plate wells were coated with human recombinant tissue transglutaminase, sample diluents contained TBS and preservative, wash buffer concentration 10× in TBS and preservatives and stop solution 0.5 M H_2SO_4. For tissue

transglutaminase IgG kit components were the same as the IgA kit except for the enzyme conjugate that contained anti human IgG peroxidase in buffer and preservative.

On the same day of analysis all sera were thawed at room temperature. tTG kits were taken outside the fridge to reach room temperature. Wash buffer was prepared by adding 100 ml of dilute to 1 liter of distilled water. Samples were diluted by adding 5µl of sample to 500 µl of sample diluents reagent. Wells coated with antigen were filled with 300 µl of wash buffer each, and soaked for about 10 seconds and then decanted. 100 µl of Calibrators, controls and diluted samples were pipette into the respective wells and incubated for 30 min at room temperature. After the incubation the plate was washed manually 3 times with 300 µl of wash buffer; excess solution was removed by tapping the inverted plate on a paper towel. 100 µl anti-human IgA or IgG peroxidase conjugated antibodies IgA or IgG to peroxidase in buffer and added into each well. Then the plate was incubated for 30 min at room temperature. Incubation solution was discarded and the plate washed as mentioned above. 100 µl of substrate containing TMB and hydrogen peroxide was added to each well and the plate incubated for 30 min at room temperature in the dark. 100 µl per well of stop solution was added and the plate tapped gently to mix the contents. Optical density was measured with photometer at 450nm (Reference-wavelength: 600-650 nm) within 30 mints after adding the stop solution.

According to the tTG IgA and IgG kits one of each negative and positive control and calibrators control should be tested along every sample batch. Controls and calibrator should be within acceptable ranges which for tTG IgA were as follows (Table 2.1), whereas, the acceptable ranges for tTG- IgG were as follows (Table 2.2)

Table 2.1: The acceptable range of tTG IgA calibrators and controls expressed as OD and U/ml.

Calibrators	**Result OD**	**Acceptable range OD**
Calibrator A	0 052	< 0. 100
Calibrator F	2.378	> 1.000
Controls	**Result U/ml**	**Acceptable range U/ml**
Positive control	25	21 - 30
Negative control	0.41	< 2.5

Table 2.2: The acceptable range of tTG IgG calibrators and controls expressed as OD and U/ml.

Calibrators	**Result OD**	**Acceptable range OD**
Calibrator A	0.049	< 0. 100
Calibrator F	2.373	> 1.000
Controls	**Result U/ml**	**Acceptable range U/ml**
Positive control	25	23 - 32
Negative control	0 77	< 2.5

The test was considered invalid when the results of controls fall outside the acceptable range. In this study the results can be expressed qualitatively, the OD of the samples was compared with the Borderline OD. The latter was determined according to the following formula absorbance OD was determined according to the following formula:

$$OD_{borderline} = OD_{positive\ control} \times factor$$

The factor depends on kit lot which was in this kit for IgA = 0.21, while for IgG was = 0.31. Then one can find the ratio of the sample by using the formula:

$$\text{Ratio} = OD_{\text{sample}} / OD_{\text{borderline}}$$

Interpreting the results for tTG IgA and for tTG IgG was based on cutoff values as follows: cutoff for the positive, equivocal and negative cases using qualitative evaluation ratio for tTG IgA >1.2, 0.85-1.2 and <0.85, respectively. Cutoff for the positive, equivocal and negative cases using qualitative evaluation ratio for tTG IgG >1.15, 0.9-1.15 and <0.9, respectively.

II.2.2 Total Human Serum IgA

Quantitative determination of human IgA in serum was done by sandwich ELISA. The test was carried out according to the instruction of the kit manufacturer (XEMA- Medica, Russia). IgA from the samples was captured by the antibodies coated onto the microwells surface, unbound material was removed by washing. Second antibody directed against another epitopes of IgA and labeled with peroxidase enzyme was then added into the microwells. After subsequent washing procedure, the enzymatic activity bound to microwells surface was detected and quantified by addition of the substrate mixture. Then the stop solution was added and the optical density was measured at 450 nm; which is directly related to the quantity of the measured IgA in the samples.

The kit contained calibrators with concentrations of 0, 0.1, 0.5, 2, 5 g/l, control, sample diluents EIA buffer, EIA buffer to be added to microwell prior to addition of diluted samples, enzyme conjugate, substrate solution containing TMB, twelve separate strips of

eight wells coated with specific antigen, wash solution concentrate 10× amount contain PBS buffer, stop solution 0.5 H_2SO_4 and a plate sealing tape.

This test was done only for the reactive and borderline tTG IgG samples with negative tTG IgA results to explore whether such discrepancy could be explained by deficiency in the total IgA. 5µl of sample was diluted with 995 µl of EIA dilution buffer. The desired numbers of microstrips were arranged into the frame, and then calibrators, control samples and samples in duplicates were added to the wells (controls and calibrators added without dilution). 120 µl of red EIA buffer was pipette into unknown sample well. 100 µl of calibrators and controls were added into allocated wells. Then 5 µl of diluted samples were added into allocated wells. The addition was made within 3 minutes to ensure a uniform incubation time for all samples. Contents of the wells were mixed by short horizontal rotating of plate for 5-7 seconds; plate was covered by plate adhesive tape and incubated for 30 minutes at 37°C. Wash buffer was prepared by adding 120 ml of distilled water to 12 ml of washing solution 10 X then the plate was washed 3 times. 100 µl of conjugate was dispensed into the wells then plate was incubated for 30 minutes at 37°C. Plate was washed 5 times then 100 µl of substrate was dispensed into the each wells. Plate was incubated for 10-20 minutes at 20-25°C. 100 µl of stop solution was pipette into the wells. Optical density was measured at 450 nm.

The data obtained quantitatively evaluated with a standard curve drawn by hand on linear graph paper. The concentrations of the 5 calibrators were 0.0, 0.1, 0.5, 2 and5 g/l. OD values of the calibrators (y-axis) were plotted against their concentration s (x-axis). Concentrations of the samples can be read directly from the standard curve.

The test was considered valid when the concentration of control sample was in the range between 0.5-2 g/l and the concentration of the calibrator 5 is not less than 1.5 g/l. Reading of the samples was obtained quantitatively from the standard curve.

II.2.3 Anti-Endomysial Antibody (EMA)

Done by using a kit based on indirect immumofluorescence antibody test for qualitative and semi-quantitative assessment of endomysial antibodies; manufactured by (IMMCO diagnostics, Buffalo, USA). Patients sera were incubated on tissue section to allow binding of antibodies to the substrate. Any antibodies not bound are removed by rinsing. Bound antibodies of the IgA or IgG class were detected by incubation of the substrate with fluorescein-labeled, anti-human immunoglobulin conjugate. The tests were examined under a fluorescence microscope equipped with appropriate filters Axiovoision 3.1, Zeiss Axcocam camera, Zeiss Co. Germany). The presence of EMA was demonstrated by an apple green fluorescence of the endomysium lining of smooth muscle bundles.

Each kit contained 8 slides each with 6 wells coated by primate smooth muscle, slides' substrate, EMA positive control human serum, EMA negative control human serum, anti-human IgA FITC conjugate with Evan's blue counterstain, sample diluents buffer, phosphate buffered saline PBS, mounting medium and cover-slips.

The test was done only for positive samples in tTG IgA and tTG IgG. On the same day of analysis all sera and reagents were placed at room temperature. Buffer diluents was ready to use, whereas, phosphate buffered saline PBS was dissolved in I liter of distilled water. Patient serums were diluted by adding 200µl of serum to 300µl of buffer diluents 1:2.5. Controls were used undiluted. Slides were removed carefully without touching the substrate

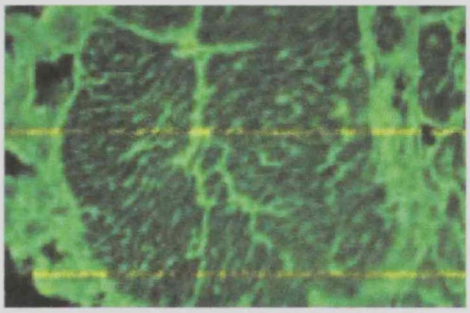
and were labeled and placed in incubation chamber lined with paper towels moistened with water to prevent drying. 50µl of negative control was applied to well number 1 and 50 µl of positive control to well number 2. Then 50µl of diluted samples were applied to other wells. Lid was placed on incubation chamber and the slide was incubated for 30 minutes at room temperature. Slide was removed from the incubation chamber, and then was rinsed in beaker filled with PBS and then transferred immediately into Coplin jar and washed for 10 minutes. Slide was removed from Coplin jar then the edge of the slide was blotted on a paper towel to remove excess PBS. Slide was placed in incubation chamber then the conjugate dropper vial was gently squeezed to apply 1 drop to each well. Lid was replaced on incubation chamber and incubated for 30 minutes at room temperature. Slide was removed from the incubation chamber and then s rinsed in beaker filled with PBS and was dipped in a beaker containing PBS to remove excess conjugate. Slide was transferred immediately into Coplin jar and was washed for 10 minutes. The excess PBS was removed by blotting as explained above. While the slide still wet coverslip was mounted by adding 3 drops of the mounting medium evenly spaced on coverslip and inverting the slide onto the coverslip. To remove any air bubble a gentle pressure was applied along the edge of the coverslip. Same steps were repeated for each slide. Slides were examined by fluorescent microscope at a magnification of 200X or greater. Negative in both IgA and IgG tests was considered as free from celiac, while positive samples would consider as serologically positive celiac disease and the patient was asked to do endoscopy.

Both negative and positive controls were included with each test run. Negative control should show no specific fluorescence of the endomysium lining of the smooth muscle bundles, whereas the positive control should give 2+ or greater staining intensity of the

tubules of smooth muscle bundles. The test should be repeated when the controls did not behave as expected.

The positive results of the tests for endomysial antibodies obtained qualitative through the intensity of the tubules of smooth muscle bundles. Were + referred to low intensity, + + referred to middle intensity and +++ referred to high intensity Endomysial antibodies react as network of the thin, irregular lines around the sarcolemma of the individual smooth muscle fibrils (figure 2.2).

Figure 2.2: EMA staining reaction on primate smooth muscle, 200× staining of lining of the smooth muscle bundles.



II.3 Statistical Analyses

Data were analyzed on personal computer using SPSS (version 15.0, SPSS Inc., Chicago, IL). The linear by linear, the Pearson chi-square test and the Fisher exact test were used to compare variables between females and males. The relationship between the variables as observed through the study questionnaire and the serodiangosis of CD was analyzed using logistic regression.

III. RESULTS

III. RESULTS

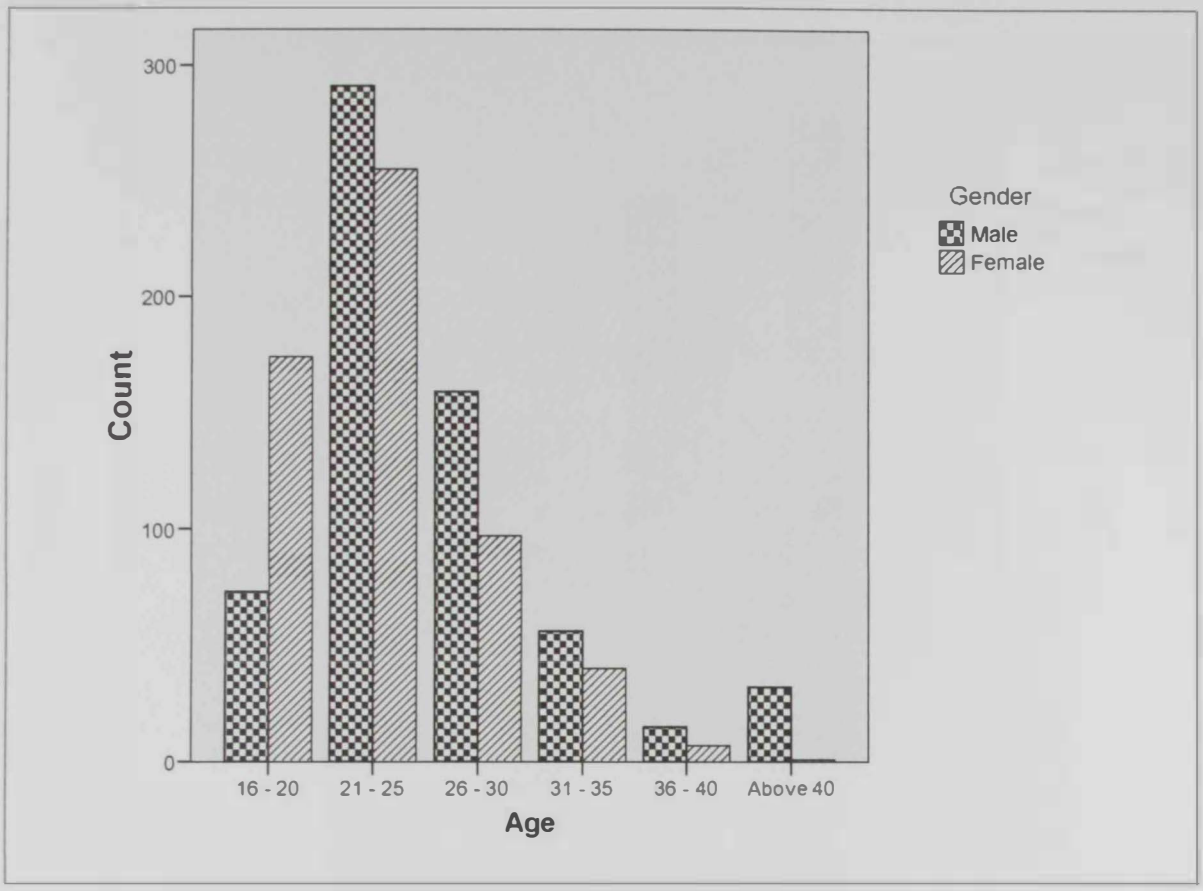
III. 1. Subject characteristics

Subjects were UAE national adult males (n = 626) and females (n = 574) who came to Al Ain Hospital for premarital tests. Collection of blood samples was carried out from September 2007 to April 2008. A total of 1430 subjects were asked to participate in the study and 1211 (84.7%) agreed. Out of those included, 11 blood samples were excluded because of been grossly hemolytic. Therefore, a total of 1200 UAE national subjects were included in the study. Sample size was calculated on the basis of 2005 Al Ain population census with estimated prevalence of CD of 1.0% and a confidence level of 95% and an estimated confidence interval of 0.58. The estimated sample number was 1150 and it was adjusted to 1200 to include about 4% more than the required number.

III.2. Demographic data

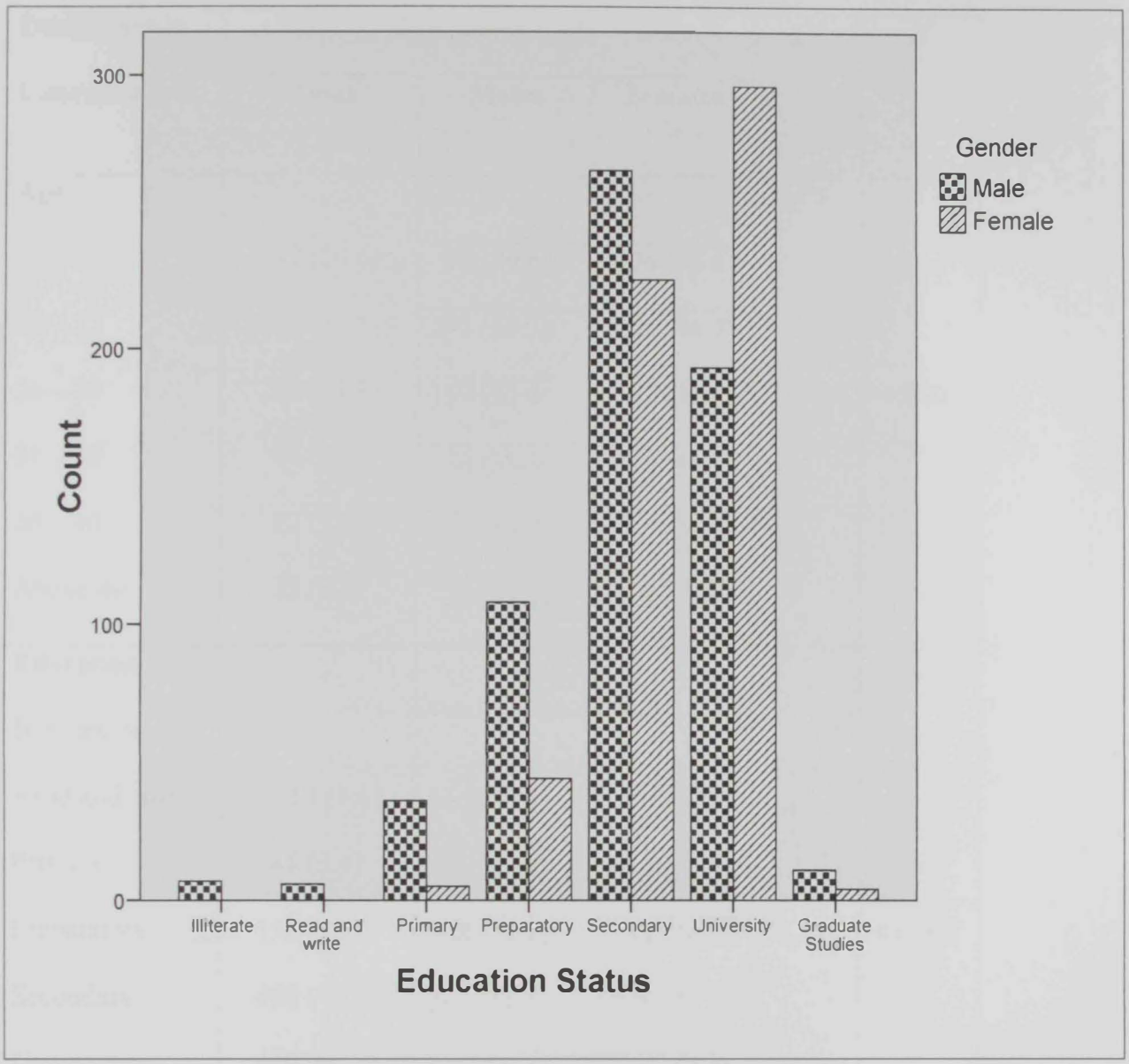
The age range of the participants was 16-70 years with a mean ± (S.D.) of 24.87 ± (6.35). The distribution of subjects into 6 age groups according to gender showed that the majority (87.4%) was between 16 and 30 years and there were more males than females except in the 16-20 years age group (Fig. 3.1).

Figure 3.1: Distribution of UAE nationals according to age.



The distribution of subjects according to education illustrates that the proportion of females who finished university education was higher compared to males (Fig. 3.2).

Figure 3.2: Distribution of UAE nationals according to educational status.



The distributions of age and education were significantly different between females and males [($\chi 2 = 71.739$; $p < 0.001$ and $\chi 2 = 74.787$; $p < 0.001$, respectively) (Table 3.1.)].

Table 3.1: Distribution of age and education according to gender among sampled subjects.

Demographic Characteristic	Frequency (%)			χ^2*	P
	Total	Males	Females		
Age					
16 – 20	247 (20.6)	73 (29.6)	174 (70.4)		
21 – 25	546 (45.5)	291 (53.3)	255 (46.7)		
26 – 30	256 (21.3)	159 (63.6)	97 (36.4)	71.739	< 0.001
31 – 35	96 (8.0)	56 (58.3)	40 (41.7)		
36 – 40	22 (1.8)	15 (68.2)	7 (31.8)		
Above 40	33 (2.8)	32 (97.0)	1 (3.0)		
Education					
Illiterate or Read and write	13 (1.1)	13 (100.0)	0 (0.0)		
Primary	41 (3.4)	36 (87.8)	5 (12.2)		
Preparatory	152 (12.7)	108 (71.1)	44 (28.9)	74.787	< 0.001
Secondary	490 (40.8)	265 (54.1)	225 (45.9)		
University	489 (40.8)	193 (39.5)	296 (60.5)		
graduate studies	15 (1.2)	11 (73.3)	4 (26.7)		

* χ^2 value is for linear-by-linear association.

III. 3 Questionnaire Data

All subjects were inquired about the following: celiac awareness, self or first degree relative previously diagnosed as CD, history of anemia, chronic headache, chronic diarrhea, diabetes, tumor, thyroid anomaly and hepatitis. Since, none of the subjects was previously diagnosed as CD patient therefore; the variable previously diagnosed as CD patient, was not included in data analysis any further.

III. 4 Serological Results

Fourteen subjects (1.2%) were positive for tTG IgA and EMA IgA, whereas the remained 1186 (98.6%) subjects were clear cut negatives for tTG IgA. Five of the above mentioned 14 subjects were also positive for tTG IgG, and only 4 of them were also positive for EMA IgG. One subject was equivocal on tTG IgG and positive in EMA IgG. The remaining 8 subjects were negative in tTG IgG and only 5 of them were positive for EMA IgG.

Of the 1186 tTG IgA negative subjects two were positive for tTG IgG and 2 were equivocal. Out of the two positives, one was negative in the two EMA tests and therefore was considered as a CD free subject. The other positive subject was also positive for EMA IgG and negative for EMA IgA. He was excluded from the data analysis because the celiac status could not be determined serologically. One of the two equivocal subjects in tTG IgG was positive for EMA IgG and negative for EMA IgA, whereas the other one showed the opposite pattern with regard to EMA i.e. negative for EMA IgG and positive for EMA IgA. Both subjects were also excluded from the data analysis for the same reason as the aforementioned excluded subject. Anemia was the most common clinically associated parameter in CD positive subjects (Table 3. 2).

Table 3.2: Anti tTG, EMA IgA and IgG antibodies in: 14 positive subjects (serologically CD silent or latent); one negative (serologically CD free) and 3 excluded subjects on the basis of undetermined CD serological status.

Subject	Gender	Age	tTG IgA† qualitative evaluation ratio	tTG IgG‡ qualitative evaluation ratio	EMA IgA	EMA IgG	Overall CD* Serology	Clinical# history
1	M	24	7.6	0.187	+ + +	+	1	a
2	F	28	1.27	0.214	+	+ + +	1	t
3	F	22	2.42	0.490	+ + +	-ve	1	n
4	F	24	3.6	1.39	+ +	-ve	1	n
5	F	23	8.25	2.2	+ + +	+ +	1	a
6	F	20	3.15	0.75	+ +	-ve	1	n
7	F	20	6.6	0.513	+ + +	-ve	1	n
8	F	22	4.87	0.914	+ + +	+ +	1	a
9	F	25	9.1	0.189	+ + +	+ +	1	n
10	F	18	9.89	1.53	+	+ + +	1	a
11	F	24	9.13	0.347	+ + +	+ +	1	n
12	F	27	7.6	0.269	+	+ + +	1	n
13	F	24	4.25	1.77	+ + +	+ +	1	n
14	F	22	6.78	4	+ +	+	1	a
15	M	23	0.60	1.04	-ve	+ + +	3	n
16	F	28	0.50	1.249	-ve	-ve	2	n
17	F	27	0.76	1.09	+	-ve	3	n
18	M	25	0.409	1.28	-ve	+ + +	3	n

†Cutoff for the positive, equivocal and negative cases using qualitative evaluation ratio for tTG IgA >1.2, 0.85-1.2 and <0.85, respectively.

‡Cutoff for the positive, equivocal and negative cases using qualitative evaluation ratio for tTG IgG >1.15, 0.9-1.15 and <0.9, respectively.

* 1= positive, 2 = negative and 3 = undetermined and excluded from further analysis.

a = anemia, t = thyroid anomaly and n = no complain.

III. 5 Association of gender and other variables with CD serology

In order to test for any association between gender and variables observed through questionnaire on one hand and CD serology on the other results of simple logistic regression analyses are presented in Table 3.3. Only celiac awareness, anemia, thyroid anomaly and gender were significantly associated with CD serology. The crude OR (95% CI) of females being seropositive for CD serology compared to males was [14.462 (1.886-110.909), $p < 0.001$].

Table 3.3: Results of simple logistic regression analyses of CD serology versus gender and anamenistic variables obtained through questionnaire.

Parameter	Frequency n (%)	CD Serology		OR (95% CI)	P[b]
		negative n (%)	positive n (%)		
Celiac Awareness					
No[a]	1183 (98.8)	1171 (99.0)	12 (85.7)		**< 0.009**
yes	14 (1.2)	12 (1.0)	2 (14.3)	16.264 (3.279-80.663)	
CD in 1st degree family member					
No[a]	1195 (99.8)	1181 (99.8)	14 (100)		0.828
Yes	2 (0.2)	2 (0.2)	0.0 (0.0)		
Anemia					
No[a]	1106 (92.4)	1097 (92.7)	9 (64.3)		**<0.003**
Yes	91 (7.6)	86 (7.3)	5 (35.7)	7.087(2.324-21.612)	
Headache					
No[a]	1185 (99.0)	1171 (99.0)	14 (100)		0.594
Yes	12 (1.0)	12 (1.0)	0.0 (0.0)		
Chronic Diarrhea					
No[a]	1192 (99.6)	1178 (99.6)	14 (100)		0.731
Yes	5 (0.4)	5 (0.4)	0 (0.0)		
Diabetes					
No[a]	1176 (98.2)	1162 (98.2)	14 (100)		0.480
Yes	21 (1.8)	21 (1.7)	0 (0.0)		

Tumor					
No [a]	1196 (99.9)	1182 (99.9)	14 (100)		0.878
Yes	1 (0.1)	1 (0.1)	0 (0.0)		
Thyroid					
No [a]	1188 (99.2)	1175 (99.3)	13 (92.9)		**<0.09**
Yes	9 (0.8)	8 (0.7)	1 (7.1)	11.298 (1.317-96.945)	
Hepatitis					
No [a]	1186 (99.1)	1172 (99.1)	14 (100)		0.610
Yes	11 (0.9)	11 (0.9)	0 (0.0)	0.000 (0.000-0.000)	
Gender					
male [a]	624(52.1)	623 (52.7)	1 (7.1)		**<0.000**
female	573 (47.9)	560 (47.3)	13 (92.9)	14.462 (1.886-110.909)	

[a] Reference group

[b] Omnibus tests of Model Coefficients

Table 3.4: Adjusted OR and 95% confidence intervals for celiac disease antibodies in UAE nationals from Al Ain.

Parameter	OR (95% CI)[b]	P
Celiac Awareness		
No	1[a]	**0.007**
Yes	10.289 (1.897 – 55.802)	
Anemia		
No	1[a]	**0.01**
Yes	4.577 (1.447 – 14.476)	
Gender		
male	1[a]	**0.026**
female	10.465 (1.333 – 82.143)	

[a] Reference group

[b] OR adjusted for celiac awareness, history of anemia, history of thyroid anomaly and gender.

The adjusted OR using multiple logistic regression for the statistically significant parameters in binary logistic regression revealed that only celiac awareness, anemia and gender were independently associated with CD serology. For gender, the adjusted OR (95% CI) was [10.465 (1.333– 82.143), $p < 0.03$] as presented in Table 3.4. The odds of CD seropositive among females are 10.465 times higher than among males. The odds of CD seropositive among those with awareness of the diseases are 10.289 times higher than among those without awareness. Moreover, the odds of CD seropositive among those with anemia are 4.577 times higher than among those without anemia.

In addition to the difference in CD serology $\chi^2 = 9.737$, $p < 0.003$, males and females UAE were also significantly different in celiac awareness, history of anemia and diabetes as presented in Table 3.5.

Table 3.5: Distribution of CD serological results and questionnaire data in adult male and female UAE nationals in Al Ain.

Parameter	Frequency n (%)	Male n (%)	Female n (%)	χ^2	p
CD Serology					
Negative	1183 (98.8)	623 (99.8)	560 (97.7)	9.737	**<0.003**
Positive	14 (1.2)	1 (0.2)	13 (2.3)		
Celiac Awareness					
No	1183 (98.8)	621 (99.5)	562 (98.1)	4.178	**< 0.05**
yes	14 (1.2)	3 (0.5)	11 (1.9)		
CD in 1st degree family member					
No	1195 (99.8)	624 (100)	571 (99.7)		0.229*
Yes	2 (0.2)	0 (0.0)	2 (0.3)		
Anemia					
No	1106 (92.4)	601 (96.3)	505 (88.1)	27.311	**<0.001**
Yes	91 (7.6)	23 (3.7)	68 (11.9)		
Headache					
No	1185 (99.0)	618 (99.0)	567 (99.0)	0.000	1.000

Yes	12 (1.0)	6 (1.0)	6 (1.0)		
Chronic Diarrhea					
No	1192 (99.6)	621(99.5)	571 (99.7)		1.0*
Yes	5 (4.4)	3 (0.5)	2 (0.3)		
Diabetes					
No	1176 (98.2)	606 (97.1)	570 (99.5)	8.34	**<0.005**
Yes	21 (1.8)	18 (2.9)	3 (0.5)		
Tumor					
No	1196 (99.9)	623(99.8)	573 (100)		1.0*
Yes	1 (0.1)	1 (0.2)	0 (0.0)		
Thyroid					
No	1188 (99.2)	622(99.7)	566(98.8)		0.096*
Yes	9 (0.8)	2 (0.3)	7 (1.2)		
Hepatitis					
No	1186 (99.1)	617 (98.9)	569 (99.3)	0.216	0.642
Yes	11 (0.9)	7 (1.1)	4 (0.7)		

* Fisher's Exact Test

The above gender differences make it plausible to test the association of questionnaire data with CD serology in females as they constitute the bulk of CD positive cases (13 out of 14). Binary logistic regression was used to test which of the questionnaire parameters associates with the CD serological results in females. Only CD awareness and history of anemia were

found to associate with anti tTG and anti EMA IgA antibodies i.e. positive serology, as shown in Table 3.6.

Table 3.6: Results of simple logistic regression analyses of CD serology versus anamenistic variables obtained through questionnaire in female subjects.

Parameter		CD Serology			
	Frequency	negative	positive	OD (955% CI)	P[b]
	n (%)	n (%)	n (%)		
Celiac Awareness					
No[a]	562 (97.7)	551 (98.0)	11 (81.8)		**0.02**
yes	11 (2.3)	9 (2.0)	2 (18.2)	11.131 (2.15-57.632)	
CD in 1st degree family member					
No[a]	571 (99.7)	558 (99.6)	13 (100.0)		0.762
Yes	2 (0.3)	2 (0.4)	0 (0.0)		
Anemia					
No[a]	505 (88.1)	496 (88.6)	9 (69.2)		**0.066**
Yes	68 (11.9)	64 (11.4)	4 (30.8)	3.444 (1.031 - 11.507)	
Headache					
No[a]	567 (99.0)	554 (98.9)	13 (100.0)		0.599
Yes	6 (1.0)	6 (1.1)	0 (0.0)		
Chronic Diarrhea					
No[a]	571(99.7)	558 (99.6)	13 (100.0)		0.762

Yes	2 (0.3)	2 (0.4)	0 (0.0)		
Diabetes					
No [a]	570 (99.5)	557 (99.5)	13 (100.0)		0.710
Yes	3 (0.5)	3 (0.5)	0 (0.0)		
Thyroid					
No [a]	566 (98.8)	554 (98.9)	12 (92.3)		0.141
Yes	7 (1.2)	6 (1.1)	1 (7.7)	7.694 (0.859 – 68.95)	
Hepatitis					
No [a]	569 (99.3)	558 (99.3)	13 (100.0)		0.668
Yes	4 (0.7)	4 (0.7)	0 (0.0)		

[a] Reference group

[b] Omnibus tests of Model Coefficients

The adjusted OR and 95% CI for celiac antibodies in relation to celiac awareness and history of anemia are presented in Table 3.7. Both parameters were independently associated with CD serology though the association for history of anemia approach statistical significance OR (95% CI) was 3.318(0.969 – 11.359); p = 0.056

Table 3.7: Adjusted OR and 95% confidence intervals for celiac disease antibodies in female subjects.

Parameter	OD (99% CI)[b]	P
Celiac Awareness		
No	1[a]	
Yes	10.565 (1.972 – 56.615)	0.006
Anemia		
No	1[a]	
Yes	3.318(0.969 – 11.359)	0.056

[a] Reference group

[b] OR adjusted for celiac awareness and anemia.

In female subjects, the odds of CD seropositive among those with awareness of the diseases are 10.565 times higher than among those without awareness. Finally, the odds of CD seropositive among those with anemia are 3.318 times higher than among those without anemia.

IV. DISCUSSION

IV. DISCUSSION

The epidemiological pattern of CD in the world has changed due to many factors e.g., more awareness of the different clinical presentation of CD and discovering of new serological tests which are simpler and inexpensive led to increase in the power of detecting many previously undiagnosed CD patients (Accomando & Cataldo, 2004). Before the new serological test the prevalence of CD was low and it was thought to affect only Europeans or their descendants (Accomando & Cataldo, 2004). With the help of new methods the prevalence increased and it reaches in some countries 1:133 (Niewinski, 2008), in spite of these efforts to detect CD, the true prevalence is still not clear.

Some prevalence studies detect the disease in blood donors such in Iran (Shahbazkhni et al., 2003), Tunisia (Mankai et al., 2006) and Brazil (Gandolfi et al., 2000). Study of blood donor population has many inherent disadvantages; blood donor prevalence does not reflect the real prevalence of the general population because most of the donors are males, while many studies indicate higher prevalence of CD among females. Moreover, anemic subjects are excluded and hence exclusion of many CD patients as anemia is one of the most important signs of the disease (Accomando & Cataldo, 2004). In Middle East there are few studies on the prevalence of CD among general population, most of the studies focused on high risk population such as those having autoimmune disease e.g. diabetes mellitus type I and autoimmune thyroiditis (Rostami et al., 2004). Some studies in the Middle Ease based on diagnosis cases and its retrospective data didn't include a large number of population (Accomando & Cataldo, 2004). To our knowledge there are no published studies on CD in the United Arab Emirates and therefore most probably this is the first CD prevalence study in UAE. This study is a cross sectional seroprevalence of CD among adult UAE nationals

undergoing obligatory prenuptial examination. The prenuptial tests include screening for HIV, hepatitis B, syphilis, and anemia profile. The target population is only adolescence and adult males and females who seem healthy at time of sampling. Choosing of this group of subjects was adequate as the aim of the study is to detect silent/latent CD in adults UAE nationals; and those healthy subjects came to the test center to give blood for the above mentioned prenuptial tests and therefore no need for much formidable effort to persuade them to participate in the study. Moreover, it is more likely to give balanced sex ratio than selecting the subjects from blood donors. The slightly more proportion of males in our study can be explained by the fact that females denied more frequently to participate in the study compared to males (data not shown). Moreover, some males came alone as they intended to marry foreigners and the prenuptial tests for non UAE nationals is not carried at the test center at Al Ain Hospital but rather in the Preventive Medicine Department.

The serological testing of the study on general population is based on many studies and criteria of diagnosis of CD. The American Gastroenterological Association AGA requires to carryout serological tests of CD before doing the endoscopy (Rostom et al., 2006). The first level of serological tests for diagnosis of CD is screening for anti- gliadins IgA and IgG. The second level of serological test is screening positive samples with EMA IgA then undergoing endoscopy. Total IgA serum is required to detect IgA deficiency and for positive samples in IgG then those samples have to be screened for EMA IgG and finally endoscopy (Gomez et al., 2001). Many studies used tissue transglutaminase IgA and IgG instead of anti gliadins which is less sensitive and specific than tTG (Tatar et al., 2004). There are controversies of using IgG instead of total serum IgA to detect IgA deficiency; many studies indicate the usefulness of using tTG IgG and EMA IgG in detecting CD in patients having IgA deficiency

(Cataldo et al., 2000; Kumar et al, 2002; Dahlbom et al., 2005). According to Rostom et al., (2002), the sensitivity of tTG IgG and EMA IgG is close to 100% in IgA deficient patients, in addition measuring total serum IgA along with the tTG- IgA or EMA IgA as first steps is preferred when IgA deficiency is strongly suspected, however, patients with diabetes mellitus type I express IgG1 isotype with normal IgA level which may explain the positive tTG and EMA IgG and normal IgA total in some cases (Picarelli et al., 2005). In this study 14 (1.2%) of the subjects were positive in tTG IgA and EMA IgA which illustrate the correlation between the results of tTG IgA and EMA IgA. 5 subjects of the 14 were also positive for tTG IgG, only 4 of them were also positive for EMA IgG. According to Dahlbom et al. , (2005) the majority of IgA sufficient patients are positive for IgA concurrently had elevated IgG in both tTG and EMA and this may be due to methodological limitation or immunological difference in the isotype response . IgA tTG seems to be directed mainly against conformational tTG epitopes and it may that IgG is directed against the same epitopes. Hence a competition between tTG IgA and IgG might take place and this competition would favor antibodies with high avidity for tTG (Dahlbom et al., 2005). 3 subjects were exclude from the positive result because one samples was negative in tTG IgA, doubtful in tTG-IgG but had week positive in EMA- IgA and negative in EMA- IgG and negative in total IgA and 2 subjects were negative in both tTG- IgA and EMA- IgA but positive in tTG- IgG and EMA- IgG and they have normal level of total IgA, since this study rely on IgA serology and only on IgG in case of total IgA deficiency. However, one study identified new celiac subgroup that positive for IgG in tTG and EMA and negative in IgA in tTG and EMA and could be explained by a different isotypic switch leading to development of B-cell clones, producing IgG1 instead of IgA (Picarelli et al., 2001).

All serological subjects belong to Arabic Bedouin families which in agreement of the study of Catassi et al., (1999) reporting that the highest prevalence of CD among Arab sub-Saharan. Based on the parameters significantly associated with celiac serology in this study, awareness of CD could be due to many factors. Most of the subjects who have information about the disease work in health service, medical students or have relative who suffer from some classic symptoms of the disease with advising from the doctors not to eat any gluten containing food. Moreover, the awareness inherent in the study itself, since the collection of the samples extended for 6 months, some subjects could have informed members of their family who themselves participated in the study at a later stage of the study.

The prevalence of CD found in this study 1: 86 among UAE nationals of Al Ain city is high comparing to prevalence reported in general population of western Europe, the prevalence in Denmark was 1:330, Finland 1:130, Germany 1:500, Italy 1:184 and Netherland 1:198 (Guandalini & Gupta, 2002). This high prevalence among UAE nationals emphasize the term CD iceberg that refers to many undiagnosed cases of CD among the general population.

In Finland a study of silent CD reported 21 serologically positive out of 2427 and 11 were females (Verkasalo et al., 2005). A study in Swedish adults found 10 positive subjects out of 1894, 7 females and 3 males (Ivarsson et al., 1999). The prevalence of in Argentina among premarital subjects was 1:167, 12 out of 2000 were positive for EMA IgA, 8 females out of 996 were positive, so the prevalence among females was double that in males (Gomez et al., 2001). In Libya among school students the prevalence was 2.24%, 15 out of 620 were positive for tTG (Alarida et al., 2006). No information about the gender of the positive cases.

Comparable results of this study in adolescents student in eastern Switzerland, 11 out of 1450 students had positive EMA and/ or tTG, 10 females out of 871 were positive and only one male. In this study despite that the number of female subjects was less than males, the prevalence among females is considered high compared to others studies in the world. According to Guiadalini, there are unknown factors increase numbers of asymptomatic CD among females, two obvious factors are the amount of gluten consumption and the extent of intestinal damage (Godfrey, 2005). There is no study comparing the consumption of wheat in females and males in UAE and this study didn't include this parameter in the questionnaire data. There are indications that autoimmune diseases share genetic risk factors and many of these loci are gender influenced (Ivarson, 2005). Females are likely to be genetically more vulnerable to environmental exposure factors that affect the immunological process leading to CD (Ivarsson, 2005).

Anemia was the main clinical sign of the celiac among of the subject, found in 5 of the positive subjects, two of the subjects suffered from chronic anemia without any diagnosis of their cases. According to the definition of world health organization anemia is a level of hemoglobin below than 13g/dl in men, below 12g/dl in non pregnant women and over the age the age 15 and, below 11g/dl in pregnant women (Ballinger, 2006). According to many studies anemia is the most single common sign of CD among adults. Study of 200 CD patients has shown 5% anemia presentation due to nutritional deficiencies (Howard et al., 2002). Thus, all patients who have anemia or iron deficiency should be screened for CD. Iron deficiency usually affects 2-5% of adolescents, adult girls and women (Ballinger, 2006).

Most of anemic subjects were females which in agreement with the finding that anemia is more common in females compared with males.

There are many limitations in this study; positive subjects refused endoscopy procedure due to many reasons, e.g. pregnancy, movement outside Al Ain city, inconvenient time for the subjects and worries from this procedure. Therefore, the study is based on serology markers of tissue transglutaminase and endomysium IgA. Moreover, the study had limited recourses and there weren't enough resources to do total IgA for all the subjects. Total IgA is a parameter required to be done at the beginning of the screening for all subjects instead of doing it only for positive tTG IgG subjects. Since the study targeted subjects undergoing prenuptial test most of the subjects were in the age range of 16-30 years of age and older subjects are underrepresented compared to the general population.

V. CONCLUSION & RECOMMENDATION

V. CONCLUSION & RECOMMENDATION

In this study gender is the most significant factor associated with CD serological results, with much higher prevalence in females (1:43) compared to males (1:621) UAE national adults from Al Ain. Those CD patients with silent/latent form of the disease may be at high risk of developing anemia, osteoporosis and all others complications associated with full blown CD later in life. The low level of awareness of the disease was probably the reason that many serologically positive CD subjects refused endoscopy procedure as a confirmatory diagnostic procedure. The result of this study should be conveyed to the health authority for raising the awareness of the disease among the health workers and the population in order to adopt fully functional program of diagnosis and treatment. There are some measures need to be done to discover as much as possible the undiagnosed cases in the general population and to increase the awareness to the disease, these measures include:

- Females who suffer from chronic anemia without knowing the reasons should be tested for CD to avoid further complication of CD.
- The results of the current study support the concept of CD iceberg which refers to the presence of many undiagnosed cases of CD among the general population. Therefore, the health workers should be aware that there are many undiagnosed cases of CD among UAE nationals. Therefore, they should refer any patients with vague symptoms, complications and/or signs suggestive of CD to be investigated as suspected CD case.
- Follow all the CD cases and run the CD diagnostic tests on all family members of diagnosed cases in order to find any undiagnosed cases within the families to prevent any future complication as much as possible.

-Make gluten free diet food available in commercial market so it is easy to the patients to find the food and to stick to the diet.

-To inform the patients that gluten not only found in the wheat and other grains but there are many commercial products that contain gluten; even some medications contain gluten.

VI. REFERENCES

VI. REFERENCES

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VII. APPENDICES

CONSENT FORM

Centre number:
Study number:
Patient ID number used in the study:

CONSENT FORM

Title of project: Screening for latent celiac disease "gluten-sensitive enteropathy" in UAE nationals adults

Names of researchers:

1. **Dr. Youssef Ali Abu-Zeid**, Ph.DC
College of Science, UAE University,

2. **Professor Miodrag Lukic**, M.D., Ph.D
College of Medicine and Health Sciences, UAE University

3. **Dr. Ali Al-Melaih Al-Fazari**
College of Medicine and Health Sciences, UAE University

4. **Waheeba Salman Jasem**
M.Sc Environmental Science Student

1	I confirm that I have read and understand the information sheet dated ..... (Version.....) for the above study and have had the opportunity to ask questions.
2	I understand that my participants is voluntary and that I am free to withdraw
3	I understand that if I withdraw from the study it will not adversely affect my healthcare or employment
4	I understand that my data will be kept confidential and in a safe place
5	I agree to take part in the above study

Name of patient	Date	Signature
Name of person taking consent	Date	Signature
Name of witness (if subject unable to read/write)	Date	Signature
Name of parent/guardian/next of kin (where subject unable to give consent due to age or incapacity)	Date	Signature

Questionnaire (استبيان)

دراسة وبائية مصلية لمرض تجويف البطن الساكن

" إعتلال معوي من الحساسية للغلوتين" لمواطني دولة الإمارات العربية المتحدة

Seroepidemiology study for latent celiac disease

"gluten- sensitive enteropathy in UAE national"

Dear attendant

This study is approved from the graduate college UAE University and Tawam Hospital. The aims of this study are to find the prevalence of latent celiac disease "gluten- sensitive enteropathy" in UAE citizen. The study requires collecting blood from you.

عزيـــــــزي المشـــــارك

هذة الدراسة تم التصريح بها من قبل جامعة الإمارات العربية المتحدة قسم الدراسات العليا و مستشفى توام و. تهدف هذه الدراسة إلى معرفة نسبة الإصابة تجويف البطن الساكن " إعتلال معوي من الحساسية للغلوتين" بين مواطني دولة الإمارت العربية المتحدة الراشدين و تتطلب الدراسة أخذ عينة دم منك

Location: **Date/ collection No:** **Sample No:**

Name: الإسم

Address العنوان

Telephone No. هاتف العمل Mobile الهاتف المتحرك

Date of Birth: تاريخ الميلاد العمر Age:

Gender الجنس : ☐ Male ذكر ☐ Female أنثى

الحالة التعليمية

Education Status ☐ read and writes يقرأ و يكتب ☐ Primary إبتدائي

☐ Preparatory إعدادي ☐ Secondary ثانوية

☐ Graduated Studies دراسات عليا ☐ University جامعي

No	Question	نعم Yes	لا No
1	هل لديك معرفة مسبق بمرض تجويف البطن؟ Have you heard before about celiac disease?		
2	هل تم تشخيص حالتك مسبقا بالإصابة بفقر الدم المزمن؟ Have You been diagnosis with chronic anemia?		
3	هل تعاني صداع مزمن ؟ Do you have chronic headache?		
4	هل سبق و شخصت حالتك بالإصابة بمرض تجويف البطن Have you been diagnosis with celiac disease before?		
5	هل سبق وشخصت حالة أحد أقربائك من الدرجة اللأولي بمرض تجويف البطن Did any one from your first degree family diagnosis with celiac disease?		
6	هل عانيت أو تعاني من إسهال مزمن Have you had or has chronic diarrhea?		
7	هل تعاني من مرض السكر Do you suffer from diabetes?		
8	هل عانيت مسبقا من أورام Have you ever had tumor?		
9	هل سبق و إن شخصت بلإصابة بأمراض الغدة الدرقية؟ Have you ever diagnosis with thyroid disease?		
10	هل سبق و إن شخصت حالتك بالإصابة بأمراض الإلتهاب الكبدي؟ Have you ever diagnosis with hepatitis disease?		

شـــــــــكرا لتعـــــــــاونكم

Thanks for cooperation

بسم الله الرحمن الرحيم

UNITED ARAB EMIRATES UNIVERSITY

جامعة الإمارات العربية المتحدة

Faculty of Medicine & Health Sciences

كلية الطب والعلوم الصحية

Department of Surgery
Fawaz Chikh Torab, M.D., Ph.D.,
Assistant Professor,
Consultant Surgeon

15 July 2007

Dr. Youssef Ali Abu-Zeid
Associate Professor
Immunoparasitology
Department of Biology
College of Science, UAE University
P.O. Box 17551, Al Ain

Dear Dr. Abu-Zeid:

Re: Al Ain Medical District Human Research Ethics Committee - Protocol No. 07/113 – Screening for Silent or Latent Celiac Disease "Gluten-Sensitive Enteropathy" in the UAE National Adults

Thank you for your letter of 30 May 2007.

Upon reviewing your correspondence the Committee feels you have adequately responded to the concerns expressed in our letter of 08 May 2007 and we hereby wish to provide you with final approval of this study.

I wish to take this opportunity to wish you every success with your project.

Should there be any ethical concern arising from the study in due course, please let the Committee know.

In the meantime, we look forward to receiving annual reports plus a terminal report. Also, for the Committee's interest and documentation, we would appreciate receiving copies of abstracts and publications should they arise.

Yours sincerely,

Dr. F. C. Torab
Deputy Chair, Al Ain Medical District Human Research Ethics Committee
/lds

الملخص

يعتبر مرض االإعتلال المعوي من الحساسية للغلوتين من الأمراض الناتجة عن عوامل بيئية و جينية و مناعية حيث تبدأ المناعة في الجسم لأشخاص تتوافر لديهم القابلية الجينية للإصابة بالمرض بمهاجمة بروتين غلوتين و المتواجد في القمح و الشعير و الجاودار في منطقة الأمعاء الدقيقة مما يودي إلى تحلل النتوءات الوعائية الموجودة على سطح الأمعاء التي تعمل على زيادة سطح الإمتصاص للمواد الغذائية و بالتالي الإصابة بالعديد من الأعراض أشهرها لإسهال و فقر الدم و الإنتفاخات المعوية. ويعتبر مرض الإعتلال المعوي من الحساسية للغلوتين من الأمراض الموثرة علي مختلف الشعوب و الأعمار في أنحاء العالم وكان يعتقد في السابق إنه يصيب فقط ذوي العرق القوقازي و تحديدا في أروبا و الولايات المتحدة الأمريكية و إستراليا و لكن توافر الفحوص المصلية و سهولة إ ستعمالها ادى الى الكشف عن العديد من الحالات الغير مشخصة في جميع أنحاء العالم و لجميع الأعراق.

و تهدف هذه الدراسة المسحية للمرض في دولة الأمارات و في مدينة العين إلى إكتشاف الحالات الساكنة و الغير مشخصة للمرض و لمعرفة نسبة تواجد المرص بين المواطنين الراشدين. و وافق على المشاركة في الدراسة 1200 شخص من القادمين للقيام بفحص الزواج في مستشفى العين و تم إجراء الفحوص المصلية على عينات الدم في كلية الطب و العلوم الصحية . أظهرت النتائج إيجابية مصلية 14 (1.2%) من المشاركين للإصابة بالمرض و لم يتم تشخيص أيا منهم مسبقا بالمرض. وأظهرت النتائج أيضا فارقا جذريا لمدى الإصابة بين الإناث و الذكور، حيث أن العدد الكلي الإصابة الإناث هو 13/573 (2.3%) يقابله إصابه واحده للذكور 1/624 (0.2%) . وتشكل هذه النتيجة إختلافا جذريا للعديد من الدراسات التي كان إختلاف الأصابة بين الجنسين ليس عاليا بهذه الصورة . و في النهاية أكدت الدراسة مصطلح قمة الثلج حيث يقابل الحالات الغير مشخصة للمرض بين أفراد المجتمع عدد قليل جدا من الحالات المشخصة و لهذا فإن المسح الوبائي للأفراد المجتمع يفيد في تشخيص و من ثم علاج الحالات الغير مشخصة.

جـامعة الإمـــارات العربية المتحدة
عمادة الدراســات العليــا
برنــامج مــاجستير علــوم البيئة

عنـــوان الرســـالة

مســـح وبـــائـــي لمـرض تجويـــف البطـــن الســـاكن "اعتلال معوي من الحساســـية للـــغلوتيـــن" بين مواطنـــي دولـــة الإمـــارات العـــربية المتـــحدة الراشـديـــن

دراسة مقدمـــة من الطـــالبـــة

وهيـــبة سلـــمان الزعـــابي

إلى

جـامعة الإمـــارات العربية المتحدة
إستكمـــالا لمتطلبـــات الـــحصول علـــى درجـــة المـــاجستير في علـــوم البيئـــة

٢٠٠٨ - ٢٠٠٩