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# Salivary and fecal microbiota and metabolome of celiac children under gluten-free diet

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ABSTRACT

Celiac disease (CD) is an inflammatory autoimmune disorder resulting from the combination of genetic predisposition and gluten ingestion. A life-long gluten free diet (GFD) is the only therapeutic approach. Dysbiosis, which can precede the CD pathogenesis and/or persist when subjects are on GFD, is reviewed and discussed. Salivary microbiota and metabolome differed between healthy and celiac children treated under GFD (T-CD) for at least two years. The type of GFD (African- vs Italian-style) modified the microbiota and metabolome of Saharawi T-CD children. Different studies showed bacterial dysbiosis at duodenal and/or fecal level of patients with active untreated CD (U-CD) and T-CD compared to healthy subjects. The ratio of protective anti-inflammatory bacteria such as *Lactobacillus-Bifidobacterium* to potentially harmful *Bacteroides-Enterobacteriaceae* was the lowest in U-CD and T-CD children. In agreement with dysbiosis, serum, fecal and urinary metabolome from U-CD and T-CD patients showed altered levels of free amino acids and volatile organic compounds. However, consensus across studies defining specific bacteria and metabolites in U-CD or T-CD patients is still lacking.
Future research efforts are required to determine the relationships between CD and oral and intestinal microbiotas to improve the composition of GFD for restoring the gut dysbiosis as a preventative or therapeutic approach for CD.

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## 1. Introduction

Celiac disease (CD) is an autoimmune condition secondary to an immunological response to ingested gluten, in genetically susceptible individuals. CD is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies (anti-transglutaninase IgA, anti-endomisial-IgA and anti-deamidated gliadin-IgA), HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy. CD is triggered by the ingestion of gliadin and related prolamins (wheat, barley and rye) that are rich in glutamine and proline residues and resist to mammalian protease digestion, creating toxic immunogenic peptides. These peptides have glutamine residues that are preferably susceptible to deamination by tissue transglutaminase (tTG). This modification makes the peptides recognizable by HLA-DQ2 molecule of antigen-presenting cells (DQ2 + or DQ8 +). In turn, DQ2 + or DQ8 + cells submit gluten peptides to CD4 + T cells that trigger the T-helper-cell type-1 response, with the consequent, gamma interferon-mediated, development of celiac lesion. The latter is represented by intraepithelial and lamina propria infiltration of inflammatory cells, crypt hyperplasia, and villous atrophy (Stepniak and Koning, 2006).

CD was thought to affect exclusively Europeans. However, it is distributed worldwide, affecting 0.6 to 1.0% of the world's population (Fasano and Catassi, 2012; Lionetti et al., 1999; Stepniak and Koning, 2006). Epidemiological studies in Africa, Middle East, Asia, and South America have shown that CD is present but mainly underdiagnosed, with areas of higher prevalence, such as the Saharawi population in North Africa where the highest prevalence of CD (5.6%) known in the world today is registered (Teresi et al., 2010). CD commonly appears in early childhood, with typical symptoms including chronic diarrhea, abdominal distension, and failure to thrive or atypical symptoms such as short stature, iron deficiency anemia, hypertransaminasemia, oral ulcers or enamel defect. However, symptoms may not develop until later in life, when the disease occurs with fatigue, weight loss, anemia, neurological symptoms and or complications (auto-immune conditions). CD is a life-long disorder and, if untreated, is associated with increased morbidity and mortality (Di Sabatino and Corazza, 2009).

Once the diagnosis is achieved, the therapeutic approach is a strict, life-long gluten free diet (GFD). However, complete exclusion of gluten is difficult due to the ubiquitous nature of this protein and cross-contamination of foods. Selected sourdough biotechnology applied for the

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production of gluten-free leavened products could be useful to eliminate gluten contamination (Di Cagno et al., 2008; Gobbetti et al., 2014). Barley glutamine-specific endoprotease, prolyl-endopeptidase from *Sphingomonas capsulata*, peptidase form selected sourdough lactic acid bacteria, prolyl-endoprotease from *Aspergillus niger* showed the capacity to digest gluten under gastrointestinal conditions (Mitea et al., 2008; De Angelis et al., 2010; Caputo et al., 2010). Indeed, alternative therapeutic options could be the oral supplementation of oligopeptidases to hydrolyze gluten immunogenic peptides.

CD commonly appears in children after the first exposures to gluten, but an increasing number of patients is also experiencing CD onset in late adulthood or adult age, suggesting that additional environmental factors could play a role in CD development (Cenit et al., 2015). An increasing number of evidences strongly indicate that oral and intestinal microbiotas play a central role in human health and disease (Claesson et al., 2012; Ling et al., 2013; Petersen, 2003; Zarco et al., 2012). A condition of dysbiosis is associated with CD patients at the diagnosis but also in remission (e.g., after two years of GFD) (for reviews see Cenit et al., 2015; Francavilla et al., 2014; Marasco et al., 2016; Verdu et al., 2015).

It was suggested that intestinal dysbiosis is strongly correlated with the pathogenesis and progression of several gastro-intestinal diseases such as dyspepsia, diarrhea, Inflammatory bowel disease (IBD), colorectal cancer (CRC), CD, and Irritable bowel syndrome (IBS) (Rautava et al., 2012). Genetic predisposition and environmental factors (e.g., diet, appendectomy, and antibiotic use) could be involved in the intestinal dysbiosis. Subjects at risk of developing CD show an association between altered microbiota and genes, which encode factors for bacterial sensing, immune reaction and metabolism. HLA-DQ2 and -DQ8 genotypes, therefore, select for pathobionts at an early stage, before the clinical onset of CD. Such an altered microbial composition also induces down-regulation of genes, which usually mark the healthy balance (Galipeau et al., 2015; Verdu et al., 2015).

Current data suggest that diet is a major driver of the composition and function of intestinal microbiota and could serve as a means of therapeutic intervention for prevention of diseases (Sonnenburg and Bäckhed, 2016; Voreades et al., 2014; Albenberg and Wu, 2014; Flint et al., 2015; Jeffery and O'Toole, 2013). GFD, per se, may affect the composition of gut microbiota and metabolome (Baranska et al., 2013; Sanz, 2010). Among different dietary components, fiber is associated to positive effects on gut microbiota and related metabolome (De Angelis et al., 2015; Sonnenburg et al., 2016; Vitaglione et al., 2015). Fibers are notably reduced in the Western diet (high in fat and simple carbohydrates, low in fibers), compared to Mediterranean diet. Overall, GFD is characterized by lower content of dietary fibers and resistant starch, compared to standard gluten-containing diet (De Palma et al., 2009; Kinsey et al., 2008; Miranda et al., 2014). Compared to a standard gluten-containing diet, healthy subjects being on GFD showed lower level of *Lactobacillus-Bifidobacterium*, along with higher number of *Enterobacteriaceae* (De Palma et al., 2009; Golfetto et al., 2014; Uy et al., 2015). In addition, GFD decreased the production of pro-inflammatory cytokines and chemokines (TNF-α, interferon-γ and IL-8) and anti-inflammatory cytokines (IL-10) by peripheral blood mononuclear cells (De Palma et al., 2009). The dysbiosis and the modification of the immunological properties suggest that CD children under GFD (T-CD) may lead to increased health risks in T-CD (Sanz, 2010; Galipeau et al., 2015).

Based on the key-role played by gut microbiota in human health, this review aims at describing the most recent advances about oral and fecal microbiota and metabolome of celiac children under GFD.

## 2. Salivary microbiota and metabolome in T-CD children

Human salivary microbiota is composed of ca. 700 bacterial species, reaching cell density of ca. 11 log CFU/g of wet weight dental plaque and 8–9 log CFU/g of saliva (Maukonen et al., 2008). Several bacterial species are involved in oral diseases, such as dental caries and periodontitis (Bik et al., 2010; Ling et al., 2010). In addition, non-oral diseases such as bacterial endocarditis (Lockhart and Durak, 1999), heart disease (Beck et al., 2005), obesity (Piombino et al., 2014), pneumonia (Paju and Scannapeico, 2007), atherosclerosis (Koren et al., 2011) and preterm low birth weight (Boggess et al., 2006) are also correlated with several oral bacteria. Saliva has recently been considered as a new tool for diagnosis of some diseases (Zarco et al., 2012).

### 2.1. The salivary microbiota associated to T-CD children

Compared to healthy individuals (HC), the salivary microbiota of T-CD children is different (Acar et al., 2012; Ercolini et al., 2015; Francavilla et al., 2014). Based on culture-dependent methods, T-CD children were characterized by the lowest prevalence of salivary mutans streptococci and lactobacilli (Acar et al., 2012) and total anaerobes, and by an increased level of *Enterobacteriaceae* (Francavilla et al., 2014). Analyzing community-level catabolic profiles, the lowest values of Shannon's diversity and substrate richness were found in T-CD children (Francavilla et al., 2014). Consistently, 16S rRNA gene-based metagenetics data showed the lowest values of richness estimator (Chao1) and diversity index (Shannon) in the saliva of T-CD children. The relative abundance of several operational taxonomic units (OTUs) differed between the salivary samples of T-CD children and those of HC. Within Firmicutes, *Lachnospiraceae*, *Gemellaceae*, and *Streptococcus sanguinis* were mainly associated with T-CD children. *Streptococcus thermophilus* markedly decreased in T-CD children compared to HC. Other Firmicutes (e.g., *Veillonella parvula*), associated with oral health (Kumar et al., 2005), were found at the lowest relative amount in the saliva of T-CD (Francavilla et al., 2014). Compared to HC, T-CD children showed a decreased level of Bacteroidetes (such as *Porphyromonas* sp., *Porphyromonas endodontalis*, and *Prevotella nanceiensis*), and a lower amount of Actinobacteria, *Actinomyces*, *Atopobium* and *Corynebacterium durum*. *Rothia mucilaginosa*, involved in gluten degradation (Fernandez-Feo et al., 2013; Zamakhchari et al., 2011), was the only Actinobacteria species higher in T-CD compared to HC children (Francavilla et al., 2014).

Recently, the salivary microbiota of fourteen T-CD Saharawi children, with biopsy-confirmed CD, and being on an African-style diet was studied (Ercolini et al., 2015). Saharawi T-CD children showed alpha-diversity indexes similar to the Italian T-CD children. However, Saharawi T-CD children showed an unusually high level of some Firmicutes (*Clostridium, Eubacterium*, *Mogibacterium*, *Catonella*, *Peptococcus*, *Filifactor*, *Peptostreptococcus*), Actinobacteria (*Actinomyces*, *Rothia*) and Tenericutes (*Bulleidia*) compared to Italian T-CD and HC children (Fig. 1) (Ercolini et al., 2015; Francavilla et al., 2014).

A characterization of the salivary microbiota of U-CD patients at the diagnosis is needed to understand the role of the salivary microbiota in the etiology of CD. Studies dealing with different severities of CD may be useful to determine the correlations between the severity of CD and the salivary microbiome.

### 2.2. Diet drives the salivary microbiota of T-CD children

In a recent attempt to understand the effect of westernization, Saharawi T-CD children were moved to Italy and subjected, for two months, to shift from the traditional African-style GFD to the Italian-style GFD (Ercolini et al., 2015). Compared to Italian-style GFD, African-style diet was richer in gluten-free cereals, legumes and vegetables, with a lower intake of animal proteins, sugars, starch and fat. Compared to African-style GFD, the relative abundance of *Granulicatella*, *Capnocytophaga*, *Porphyromonas* and *Neisseria* was higher after 30 and, especially, 60 days of Italian-style GFD, altering the 'salivary type' of the individuals (Fig. 1). As shown by partitioning around medoid (PAM) clustering, using the relative abundance of core genera, Italian HC and T-CD and Saharawi T-CD children salivary samples were grouped into three "salivary types" (Ercolini et al., 2015). The salivary

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