Title: Govind Makharia
Professor
Dept of Gastroenterology & Human Nutrition
All India Institute of Medical Sciences
New Delhi, India

Update on celiac disease

Disclosure of Interest: Nothing to Disclose
What is celiac disease?

• An chronic autoimmune enteropathy
• Multisystem disease
• Genetically susceptible individuals
  – HLA-DQ2, -DQ8 (Many more genes)
• Immunogen: Gluten
• Villous atrophy, malabsorption
• Life long disease
Celiac disease: Global trend

• Initially thought to be limited to Western Europe
• Recognized and increasing all across the globe
• Affects approx. 1% of the world’s population

CeD is increasing in USA

Riddle et al, AJG 2012

Catassi C et al, Ann Med 2010
Celiac disease epidemiology beyond the Western world
Celiac disease in Southern and East Asia

Uncommon or rare disease

An increase in the recognition of CeD has been observed in some Asian nations
Prevalence of CeD in countries in Asian region

Unknown in Majority

Cummins AG, J Gastroenterol Hepatol. 2009
Publications

Results by year

PubMed

Increasing number of publications in past 10 yrs
PubMed: 20421

Asia: 382
India: 295
China:

PubMed, Aug 2014
Hospital-Based studies: India

• Mostly from Northern part of India: So called Celiac belt
• Initially only children (Only by Pediatricians, only a few)
• Now adults also, even elderly

First time diagnosis at >50 yrs: 9%
Celiac Disease Clinic, AIIMS
Singh P, Dig Liver Disease 2013
At our center in New Delhi

Number of patients with Celiac Disease at AIIMS pediatric gastroenterology clinic

Serological tests were introduced

Children patients

Adult patients
Prevalence of celiac disease in the northern part of India: A community based study
Govind K Makharia,* Anil K Verma,* Ritvik Amarchand,† Shinjini Bhatnagar,‡ Prasenjit Das,§ Anil Goswami,† Vidyut Bhatia,‡ Vineet Ahuja,* Siddhartha Datta Gupta‡ and Krishnan Anand†
Departments of Gastroenterology and Human Nutrition*, Pediatrics† and Pathology‡, Centre for Community Medicine,† All India Institute of Medical Sciences, New Delhi, India

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Corrected seroprevalance (95% CI)</th>
<th>Corrected prevalence of CeD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (n = 6845)</td>
<td>1.10% (0.86 1.37)</td>
<td>0.85% (0.64 1.09)</td>
</tr>
<tr>
<td>Children (n = 3643)</td>
<td>2.06% (1.62 2.57)</td>
<td>1.41% (1.04 1.84)</td>
</tr>
<tr>
<td>Males (n = 5305)</td>
<td>1.28% (1.00 1.62)</td>
<td>0.91% (0.67 1.20)</td>
</tr>
<tr>
<td>Females (n = 5183)</td>
<td>1.60% (1.28 1.98)</td>
<td>1.20% (0.92 1.53)</td>
</tr>
</tbody>
</table>

Prevalence: 1.04%; One in 96
Sero-prevalence: 1.4%
Community based prevalence (Northern India, Ludhiana): 1 in 310 (3-17 yrs school children)


Expected no of patients with celiac disease in India

Approx 4-8 million
Prevalence of CeD in Asian region

Regional differences

Is it dietary factor?
People are genetically protected?
Pan-India prevalence study and Identification of reasons for differences: ICMR Task Force

Recruitment of patients (Representative population from the respective area)

- Southern part: N=9000
- Northern part: N=7000
- North Eastern: N=9000

House to house visit
Questionnaire based survey
Screening

- Anti tTG Ab Test
- HLA Test (DQ Locus genotyping) 200 individuals

Study completed
Data being analysed
Pan India: Sero-prevalence

Haryana
Total sample : n= 6209
1\textsuperscript{st} ELISA +ve : n=556 [9%]
2\textsuperscript{nd} ELISA +ve : n= 75 [1.2%]

Assam
Total sample : n= 8149
1\textsuperscript{st} ELISA +ve : n=637 [7.8%]
2\textsuperscript{nd} ELISA +ve : n= 70 [0.9%]

Tamilnadu
Total sample : n= 9000
1\textsuperscript{st} ELISA +ve : n=516 [5.7%]
2\textsuperscript{nd} ELISA +ve : n= 712 [0.13%]

HLA DQ-2/DQ-8 allele frequency: 35%
Celiac disease in other parts of Asia
# Emergence of CeD in China

<table>
<thead>
<tr>
<th>Author</th>
<th>Province</th>
<th>Patients</th>
<th>Criteria for diagnosis</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu J 2010, Rev Esp Enferm Dig.</td>
<td>Nanjing</td>
<td>IBS_D (72) IDDM (6)</td>
<td>IgA-AGA IgA-TTG</td>
<td>6/78 (AGA+) 2/78 (tTG+)</td>
</tr>
<tr>
<td>Wang XQ, 2010 Zhonghua Er Ke Za Zhi.</td>
<td>Shanghai</td>
<td>Chronic diarrhea</td>
<td>Clinical symptoms Duodenal Bx</td>
<td>14/118 suspected</td>
</tr>
<tr>
<td>Xin-Qiong W, JPGN, 2011</td>
<td>Shanghai, Wuhan, Jinan, Chengdu</td>
<td>Children with Chr diarrhea</td>
<td></td>
<td>14/118</td>
</tr>
</tbody>
</table>

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**Invited Commentary**

Another Brick in the (Great) Wall: Celiac Disease in Chinese Children

*C. Catassi and †K. Alarida*
### Only 11 suspected CeD in past 30 yrs in Japan

<table>
<thead>
<tr>
<th>Yr</th>
<th>Diagnosis</th>
<th>n</th>
<th>Gluten Challenge Test or GFD</th>
<th>Serological Test</th>
<th>Biopsy Confirmed</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Celiac sprue, Gluten induced enteropathy</td>
<td>1</td>
<td>Yes (Gluten challenge, GFD)</td>
<td>No</td>
<td>Yes (villous atrophy)</td>
<td>No</td>
</tr>
<tr>
<td>1991</td>
<td>Celiac sprue</td>
<td>4</td>
<td>Yes (Gluten Challenge)</td>
<td>No</td>
<td>Yes (villous atrophy)</td>
<td>No</td>
</tr>
<tr>
<td>1988</td>
<td>Celiac disease</td>
<td>2</td>
<td>Yes (GFD)</td>
<td>No</td>
<td>Yes (villous atrophy)</td>
<td>No</td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Celiac sprue</td>
<td>1</td>
<td>Yes (GFD)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2003</td>
<td>Celiac disease</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2006</td>
<td>B-cell Lymphoma associated with celiac disease</td>
<td>1</td>
<td>No</td>
<td>positive for tTG</td>
<td>Yes (villous atrophy)</td>
<td>Yes (nonDQ2/8)</td>
</tr>
<tr>
<td>2007</td>
<td>T-cell Lymphoma associated with celiac disease</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>Yes (villous atrophy)</td>
<td>No</td>
</tr>
</tbody>
</table>
IBD: anti-tTG Ab and anti-DGP Ab: 22 (12.8%) and 23 (13.4 %) Controls (n=172): and 3 (1.6%) and one (0.5%),

Watanabe; J Gastroenterol 2014
Pilot study: Malaysia (Multiracial country)

- Healthy young volunteers (18-40 yrs): 562
- **Screening: Anti-tTG ab, if positive EMA**
- Diagnosis of CeD: Double serology positive
- Double serology positive 16 (2.85%)
- None had symptoms

Seroprevalence of CD in healthy young adults in Malaysia: 2.85% (3 in 100).
CD is underdiagnosed, could be a much greater

Unpublished, Personal communication
## CeD in other parts of Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Report</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>A case report, RCD in a Chinese pt</td>
<td>Lok, J Dig Dis 2008</td>
</tr>
<tr>
<td>Philippines</td>
<td>No systemic report</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>No systemic report</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>No systemic report</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>No systemic report</td>
<td></td>
</tr>
</tbody>
</table>
CeD is common in India
Cases in China, Japan, Malaysia, Pakistan
What are the predictions?
Two essential requirements

HLA-DQ2 and/or -DQ8)

40% genetic susceptibility
60%: Unknown
The Grain Family Tree

Gramineae

Festucoideae
- Triticeae
  - Triticum
    - Wheat
    - Barley
    - Rye
  - Hordeinae
    - Hordeum
    - Oats

Panicoideae
- Aveneae
  - Avena
    - Oats
- Oryzeae
  - Oryza
    - Rice
- Andropogoneae
  - Zea
    - Corn
- Paniceae
  - Sorghum
    - Pennisetum
    - Sorghum
    - Millet
Wheat: A preferred cereal (10-12% protein, 80% gluten)

- Monomeric gliadins
  - ω-gli
  - α-gli
  - γ-gli
  - β-gliadins

- Polymeric glutenins
  - LMW subunits
  - HMW subunits

Solubility in aqu alcohol

- Soluble
- Insoluble

• Gliadins & glutenins: Non-covalent bonds (H bonds, ionic bonds and hydrophobic bonds)
• Important for the aggregation of and implicate structure
The origin of bread wheat: Fertile crescent

The wild relatives of bread wheat, *Triticum aestivum*, still grow in the Middle East.
Evolution of wheat: Diploid to Hexaploid

Cultivated as Einkorn wheat AA

A wild diploid wheat T. Monococcum AA

A wild diploid wheat possibly T.searsii BB

X

(Chromosome doubling)

Wild tetraploid wheat T.turgidum AA BB

A wild diploid wheat T. tauschii DD

X

(8000 yrs ago)

Cultivated 10,000yrs as Emmer wheat AA BB

Hexaploid wheat T. aestivum AA BB DD

Hexaploid
Is CeD really uncommon in Asia?
Frequency of HLA-DQ2 in the population of various countries in the Asia–Pacific region

<table>
<thead>
<tr>
<th>&lt; 5%</th>
<th>5-20%</th>
<th>&gt;20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook Islands</td>
<td>China</td>
<td>Australia</td>
</tr>
<tr>
<td>Indonesia</td>
<td>India</td>
<td>Iran</td>
</tr>
<tr>
<td>Japan</td>
<td>Malaysia</td>
<td>Israel</td>
</tr>
<tr>
<td>Korea</td>
<td>Mongolia</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Nauru</td>
<td>Singapore</td>
<td>Pakistan</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>Sri Lanka</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>Taiwan</td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>Thailand</td>
<td></td>
</tr>
<tr>
<td>Samoa</td>
<td>Turkey</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wheat consumption (kg) per person per year for countries in the Asia–Pacific region.

Cummins AG, J Gastroenterol Hepatol. 2009
Trends in Food Intake 1910 to 2011
(Per capita per day, National Average)

Rice
Wheat

National Health and Nutrition Survey Japan, 2010
The Tip of the “Celiac Iceberg” in China: A Systematic Review and Meta-Analysis

Juanli Yuan¹,², Jinyan Gao³, Xin Li¹,³, Fahui Liu¹, Cisca Wijmenga⁴, Hongbing Chen¹,⁵*, Luud J. W. J. Gilissen⁶

- MEDLINE database and four Chinese full-text databases (CNKI, CBM, VIP and WANFANG)
- Two HLA allele frequency net databases and Chinese Statistics Yearbook databases

Wheat statistics in China (1000mt)

Consumption of wheat is over 100 million metric tons for over 1,370 million people

Per capita annual consumption of wheat
Rural households: 59.6kgs
Wheat flour in urban households: 12.5 kg

Wheat consumption pattern in China

Change in dietary pattern

- Increasing demand for convenience foods
- Urbanization
  - Migration of people from rural to urban area
  - Change in traditional eating practices to breads, pasta, pizza and burger
- By June 2013, 4,000 KFC restaurants and 1,700 McDonalds in China
Frequency of HLA-haplotype and antigen

**HLA Haplotype**

**HLA antigen**

**Yuan J, PLoS, 2013**
HLA DQB1*0201/0202 allele

Ethnic minorities

Both the initials reports and presence of predisposing factors highlight that Celiac disease exists in many Asian countries.
Clinical presentation

- Classical: Gastrointestinal
- Non-classical: Non gastrointestinal
Hematologists
Pediatrician
Gastroenterologist
Hematologists
Endocrinologists
Dentist
Dermatologist
Neurologist

Failure to thrive
Irritability
Chr/intermitt diarr
Malabsorption
Anemia
Growth retardation
Anemia

Multi-system disease

Seizures
Cerebellar ataxia
Almost half of patients do not have diarrhea

3-11% of pts with anemia have celiac disease

Short statured: 2-15% are due to CeD

3-6% of patients with IBS have CeD

Liver abnormalities in celiac disease

Osteopenia and osteoporosis
How to make a diagnosis?
Basis of Diagnosis

- Demonstration of adaptive immunity to gluten: Serology
- Demonstration villous abnormality
- Response to gluten free diet
### What are the tests available?

<table>
<thead>
<tr>
<th>Serological tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA anti-gliadin ab</td>
<td>46–87%</td>
<td>70–98%</td>
</tr>
<tr>
<td>IgG anti-gliadin ab</td>
<td>42–93%</td>
<td>84–97%</td>
</tr>
<tr>
<td>Anti-endomysial ab</td>
<td>74–100%</td>
<td>99–100%</td>
</tr>
<tr>
<td>IgA anti-tissue transglutaminase ab</td>
<td>81–100%</td>
<td>97–99%</td>
</tr>
<tr>
<td>IgA anti deamidated peptide ab</td>
<td>75–78%</td>
<td>95–100%</td>
</tr>
<tr>
<td>IgG anti deamidated peptide ab</td>
<td>65–71%</td>
<td>95–98%</td>
</tr>
</tbody>
</table>
## Anti-tTG ELISA tests

<table>
<thead>
<tr>
<th>ELISA Kits</th>
<th>Cut-off U/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aesku</td>
<td>15</td>
</tr>
<tr>
<td>Binding Site</td>
<td>4</td>
</tr>
<tr>
<td>BMD Luminex</td>
<td>15</td>
</tr>
<tr>
<td>Euroimmun</td>
<td>20</td>
</tr>
<tr>
<td>Eurospita</td>
<td>7</td>
</tr>
<tr>
<td>Generic assays</td>
<td>20</td>
</tr>
<tr>
<td>Genesis</td>
<td>7</td>
</tr>
<tr>
<td>Immco</td>
<td>20</td>
</tr>
<tr>
<td>Inova</td>
<td>20</td>
</tr>
<tr>
<td>Orgentec</td>
<td>10</td>
</tr>
<tr>
<td>Phadia ELIA</td>
<td>7</td>
</tr>
<tr>
<td>Phadia</td>
<td>3</td>
</tr>
</tbody>
</table>

Wide kit to kit variation
Population sp cutoff
Low titre: Less reliable
EMA: More reliable
Serology:
Challenges in Asia Pacific region

• Availability of diagnostic kits
• Population specific cut-off value for a positive test
• Variations between different kits
Normal biopsy

- Villus crypt ratio: 3-5:1
- In duodenal bulb: a ratio of 2:1 may be accepted.
- Intraepithelial lymphocytes (IELs): 1 for 5 enterocytes
  - ULN IEL counts: 40 /100 enterocytes
  - Currently the upper limit is considered to be around 25 IELs /100 enterocytes

Pellegrino et al. Aliment Pharmacol Ther. 2011;33:697-706
### Histology: Villous atrophy

**Oberhuber modified Marsh classification 1999**

<table>
<thead>
<tr>
<th></th>
<th>Marsh 0</th>
<th>Marsh 1</th>
<th>Marsh 2</th>
<th>Marsh 3</th>
<th>Marsh 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IELS</td>
<td>$\leq 30/100$ EC</td>
<td>&gt;$30/100$ ECs</td>
<td>&gt;$30/100$EC</td>
<td>&gt;$30/100$ ECs</td>
<td>&gt;$30/100$ EC</td>
</tr>
<tr>
<td>Crypt Hyperplasia</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>C:V</td>
<td>1:3</td>
<td>1:3</td>
<td>1:3</td>
<td><strong>3a</strong>: Mild VA</td>
<td><strong>3c</strong>: Severe VA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>3b</strong>: Moderate VA</td>
<td><strong>villous atrophy</strong></td>
</tr>
</tbody>
</table>

**Legend:**
- **Marsh 0**: Normal
- **Marsh 1**: Immune cell hyperplasia
- **Marsh 2**: Villous hyperplasia
- **Marsh 3**: Villous atrophy
- **Marsh 4**: Sterile atrophy
• Increase awareness amongst pathologists
• Training of staff in handling mucosal biopsies
Who should be screened for CeD?

- Chronic/intermittent diarrhea,
- Iron-deficiency anemia,
- Failure to thrive, stunted growth
- Delayed puberty, amenorrhea
- Persistent fatigue
- Recurrent aphthous stomatitis
- Dermatitis herpetiformis
- Fracture/osteopenia/osteoporosis
Who should be screened for CeD?

First-degree relatives
Type 1 diabetes mellitus
Autoimmune thyroid disease,
Autoimmune liver disease,
Down syndrome,
Turner syndrome,
Selective IgA deficiency

- Female infertility
- Unexplained transaminase elevation
- Neurological diseases (neuropathy, ataxia)
Suspected CeD

IgA Anti-tTG Ab or IgA-anti-endomysial ab

Positive

Duodenal biopsy

Normal

Marsh I, II

HLA DQ2/DQ8 +ve

Potential CeD

Marsh III

Review

CeD

IgG serology
IgG AGA
IgG Anti-DGP ab

Response to GFD

Definite CeD

Negative

Estimate S. IgA

Low S. IgA

IgG serology
IgG AGA
IgG Anti-DGP ab

Normal S. IgA

Evaluate for other Causes
Management
Willem Karel Dicke (1905 – 1962)

PhD – Thesis 1950

First patient on GFD 1933
Gluten free diet

Under care of a nutritionist/dietician

Holistic approach
Gluten-free diet

Philosophies

- Limited detectable gluten
  - Codex Standards (1 Jan 2012)
    - ‘Gluten-free’ <20 ppm (mg/kg)
    - ‘Very low gluten’ <100 ppm
- Zero-tolerance gluten (most of US, Canada)
  - Cannot be derived from a gluten-containing grain
How much gluten

How much gluten is toxic?

50 mg can induce Villous atrophy

How much gluten, we take:

Western diet: 20-25g
Indian: varies
Bread slice (40g): 2.8g gluten
GFD most effective and the best, *but*

- Gluten ubiquitous
- Complete avoidance very difficult
- Home made food
  - Limits mobility, palatability, social isolation
  - Feeling of incompleteness
- Readymade GFD: not easily available
  - Expensive
- Limits mobility
Keys to successful GFD

Patient

Advocacy organisation

Quality information & support

Food

Excellence in food labelling

Healthcare professional

Specialist dietician

Interested doctor

Active participation
How to monitor response to therapy?
How to monitor response to therapy?

• Lifelong adherence to GFD:
  – 45%- 80 % reported to adhere strictly

• Parameters to be assessed
  – Dietary compliance
  • Disease status
  • GI symptoms evaluation
  • Optimizing growth and development
  • Look for associated diseases / conditions
  • Quality of life
  • Lab tests

Freeman HJ et al WJC, 17 , 2011
Non responder

- Non compliance with diet
- Inadvertent ingestion of gluten
- Synchronous disorders: IBS, microscopic colitis, lactose intolerance,
- Pancreatic insufficiency
- SIBO
- Erroneous diagnosis
- Complications of CeD
  - Refractory sprue,
  - ulcerative jejunitis
  - Intestinal lymphoma
Asia Pacific issues
Measures to increase awareness

• Establish prevalence of CeD across the region:
  – High-risk, hospital based
  – Population studies
Awareness about CeD should be increased amongst medical practitioners and patients

- Emphasis during undergraduate and postgraduate curriculum
- Discussion during conferences and CMEs
- Focus on primary care physicians
- Training of pathologists
Developing the infrastructure to enable successful management of CeD

• Major impediments to the successful gluten-free diet
  – Training of dieticians
  – Gluten-free infrastructure in the food supply:
    – Labelling of food
• Although absolute number of patients with celiac disease at present is not very large, the absolute number is however, expected to increase markedly over the next few years/decades.