Coeliac disease: emerging in China?

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Insulin resistance, viral load and response to peginterferon and ribavirin in patients with chronic hepatitis C virus infection

We read the article by Moucari *et al* in *Gut* recently[1] with great interest. The authors concluded that insulin resistance (IR) is correlated independently with serum hepatitis C virus (HCV)-RNA and frequently encountered in patients with HCV genotype 4 (HCV-4) infection. Also IR is a major predictor of response to peginterferon and ribavirin in 108 HCV-4 patients receiving a 48-week course of peginterferon plus ribavirin.

In our previous study we enrolled 330 Taiwanese patients with chronic hepatitis C (CHC) (150 HCV genotype 1 (HCV-1) and 180 genotype non 1 (HCV-non 1) to evaluate the association between homeostasis model assessment of IR (HOMA-IR) and response to therapy.[2] We checked the association between HOMA-IR and serum HCV-RNA level. The mean serum HCV RNA levels were similar between high HOMA-IR (>2.5) and low IR (≤2.5) in all 330 patients (5.25±1.14 vs 5.19±1.00 log IU/ml, p= 0.117) and in 150 HCV-1 patients (5.56±0.94 vs 5.36±0.99 log IU/ml, p= 0.417). The mean serum HCV RNA level was lower between high HOMA-IR (>2.5) and low IR (≤2.5) in 180 HCV-non 1 patients with borderline statistical significance (4.97±1.23 vs 5.05±0.99 log IU/ml, p= 0.056). When using HOMA-IR 2 as a cut-off of high and low HOMA-IR as Moucari *et al*, we found the mean serum HCV RNA levels were similar between high HOMA-IR (>2) and low IR (≤2) in all 330 patients (5.26±1.12 vs 5.18±1.00 log IU/ml, p= 0.260) and in 150 HCV-1 patients (5.54±0.94 vs 5.36±1.00 log IU/ml, p=0.464). The mean serum HCV RNA level was lower between high HOMA-IR (>2) and low IR (≤2) in 180 HCV-non 1 with borderline statistical significance (5.04±1.20 vs 5.02±0.98 log IU/ml, p=0.067). Since Moucari *et al* elucidated that the IR was correlated independently with serum HCV-RNA in HCV-4 patients, whether there is association between HOMA-IR and different HCV genotypes needs further studies.

Moucari *et al* reported that IR is a major predictor of response to peginterferon and ribavirin in HCV-4 patients, which indeed meets with applause. We have found that HOMA-IR was associated with SVR to peginterferon plus ribavirin in HCV-1 patients, but not in HCV-non 1 patients. Romero-Gomez *et al*[3] and Conjeevaram *et al*[4] have also reported the high HOMA-IR impairs the response to combination therapy in HCV-1 patients in different countries and all the studies strengthen the important role of IR on the response to anti-HCV combination therapy in HCV-1 and -4 patients. By the way, the HCV viral load was an independent factor, in addition to HOMA-IR, associated with SVR in HCV-1[2 4] patients. In HCV-4 patients Kamal *et al* reported that the viral load was highly correlated with and the best predictive marker for peginterferon plus ribavirin responsiveness.[5] It is noteworthy that Moucari *et al* reported the HOMA-IR rather than the HCV RNA level is a predictor of viral response in HCV-4 patients which minimised the role of pretreatment HCV RNA level on the viral response when taking the HOMA-IR into consideration in HCV-4 patients.[1] We just wonder whether the association between the HOMA-IR and HCV RNA level still exists in these 108 HCV-4 patients? On the other hand, the impact of HOMA-IR on SVR rate was especially discovered among patients with HCV-1 infection and high serum HCV RNA level (defined as 'difficult-to-treat' patients) in our previous study. It seems interesting that whether this finding can also be depicted among the HCV-4 patients in the study of Moucari *et al*.

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Coeliac disease: emerging in China?

We read with interest the leading article by Hunt and van Heel on recent advances in coeliac disease (CD) genetics.[1] They suggested that further investigation of the coeliac-associated single nucleotide polymorphisms (SNPs) in other populations was needed. Our recent work may help to push this research work in the Chinese population. Here we report on a serological screening for CD in China. CD has been historically considered to be absent in the Far East (China, Japan, Korea, Malaysia, etc.).[2] However, since the major known risk factors for CD are common in China, we used serological tests for immunoglobulin G (IgG) antigliadin antibodies (AGAs) and IgA anti-tissue transglutaminase antibodies (tTGs) to screen for CD in high risk patients,[3 4] comprising 73 cases of diarrhoea-predominant irritable bowel syndrome (IBS-D) and five cases of insulin-dependent diabetes mellitus (IDDM), 30 women and 48 men, mean age 50±15 years old. Patients with IBS fulfilled symptom-based diagnostic ROME II criteria and in addition had loose stools with undigested food, frequent stools after eating

Table 1 Seven seropositive suspected CD cases out of 78 high risk patients

Case	Gender	Age (years)	AGAs (IgG U/ml)	tTGs (IgA U/ml)
Case 1	Male	64	27.6	Negative
Case 2	Female	20	30.3	Negative
Case 3	Male	20	50.1	Negative
Case 4 (IDDM)	Female	37	28.8	Negative
Case 5	Female	55	12.2	Negative
Case 6	Female	64	26.7	9.6
Case 7	Male	26	Negative	8.6
Positive control	Unknown	Unknown	69.5	50.9

AGA, antigliadin antibody; CD, coeliac disease; IDDM, insulin-dependent diabetes mellitus; Ig, immunoglobulin; tTG, antitissue transglutaminase antibody

fatty food, fatigue, pale tongue and thin tongue coating, and a thready pulse. All patients were adult Han Chinese living in Jiangsu province with wheat products in their diets. These patients visited Jiangsu provincial hospital of TCM between December 2002 and August 2005. The results showed that 6 out of 78 patients (7.7%) were positive for IgG AGAs, and 2 (2.6%) were positive for IgA tTGs (table 1). Total IgA measurement excluded IgA deficiency. Follow-up has demonstrated that these serologically positive patients did not want to have an invasive diagnosis by duodenal biopsy but preferred to have a gluten-free diet (GFD). In China, rice and wheat are mainly consumed as human food staples and hence it is convenient for Chinese people to switch to a GFD. In two persons (cases 3 and 5) who accepted a GFD for 1 year, diarrhoea stopped. Case 3 started to thrive and case 5 stopped losing weight.

Our serological screening demonstrated that CD might exist in Jiangsu province. This province is one of the main wheat-producing areas in China.[5] The CD-predisposing human leucocyte antigen (HLA)-DQ alleles, accounting for ~30% of heritability in Caucasians, are not rare in Han inhabitants of this area. Their frequency of haplotype DQA1*0501-DQB1*02 (DQ2) is 7.2% and of DQA1*03-DQB1*0302 (DQ8) is 4.7%, and the frequencies of haplotypes DQA1*02-DQB1*02 and DQA1*05-DQB1*03 together capable of encoding DQ2 *in trans* are 9.4% and 7.8%, respectively.[6] Even though there were no serological test results, Jiang *et al* had reported four cases of CD by duodenal biopsy this year in Zhejiang province which is neighbour of Jiangsu.[7] The results of our research are encouraging. Considering the increasing gluten intake,[5] frequency of common HLA-DQ2/DQ8 alleles and the large population size of Jiangsu province, we speculate that CD might not be rare.

The next step is to perform a serological screening test for more susceptible patients in high risk populations and general populations. Biopsy of serum-positive patients is the cornerstone of diagnosis and it should be verified by a GFD. HLA-DQ genotyping, CD genome-wide association studies and fine mapping for diagnosed Chinese patients as suggested by Hunt and van Heel[1] will help to supplement present knowledge of CD. Just like other multifactorial diseases,[8] we might gain much new information by transracial gene mapping in non-European populations.

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Low Foxp3 expression in negative sentinel lymph nodes is associated with node metastases in colorectal cancer

In a recent commentary, Sobhanu and Le Gouvello,[1] take advantage of the account of Chaput *et al*[2] of a new population of T regulatory (Treg) lymphocytes ($CD8^+$) to address the more general question of whether accumulation of Tregs (both $CD8^+$ and conventional $CD4^+$) must be considered a prognostic factor in colorectal cancer (CRC). Tregs ($Foxp3^+$) play a pivotal role in maintaining immune system homeostasis through their ability to suppress immunological responses, including tumour immunity against tumour-associated antigens. In their interesting commentary, Sobhanu and Le Gouvello[1] argue that the in vivo immunosuppressive effect of these cells in CRC still remains controversial. Actually, accordingly to the available data, we believe it reasonable to state that $CD4^+$ Tregs do not contribute to CRC escape from host immunity. While earlier studies showed a higher density of tumour-infiltrating Tregs in advanced compared with early disease,[3 4] an opposite pattern was reported in later studies.[5 6] Correlation of Foxp3 staining with favourable clinical outcome was also suggested[5] and has recently been statistically proved in two independent studies The first study involved 967 patients with stage II and stage III CRC,[7] whereas in the second study patients with CRC were stratified according to their mismatch repair (MMR) status. MMR-proficient patients were further stratified according to the frequency of tumour-infiltrating $Foxp3^+$. A high frequency of Foxp3 was associated with increased 5-year survival rate.[6] Concomitant high frequency of Foxp3 and tumour regression indicate that, in the context of the CRC, Tregs are not

Table 1 Relationship between Foxp3 expression in sentinal lymph nodes (SNs) and pTpN staging

	Number of cases and pT	pN0	pN1/pN2	Fisher exact test
$Foxp3^+$ cells in SN >10%*	21 (18 pT2 + 3 pT3)	21	0	χ^2=13.58p=0.0001
$Foxp3^+$ cells in SN <10%	9 (9 pT3)	3	6	

*The numbers of $Foxp3^+$ cells present within the SN were counted manually in three high-powered fields (HPFs) by two independent pathologists, and a threshold of 10% FoxP3-positive cells/HPF was selected to define a FoxP3-positive case.