allowing HOMA to be used with either immunoreactive insulin or specific insulin assays, and a model of renal glucose losses, allowing its use in more hyperglycemic states. These modifications provide a more accurate representation of physiology and successfully predict the homeostatic responses to an intravenous glucose infusion. The use of the current HOMA model performs well in comparison with several tests of insulin sensitivity, including the intravenous glucose tolerance test, and with minimal model analysis and the short insulin tolerance test of Bonora (6) and tests of β-cell function (7), including the hyperglycemic clamp (8), the oral glucose tolerance test (9), and the frequently sampled intravenous glucose tolerance test (FSIVGTT) (7).

Second, the model has been incorporated in a simple MS-DOS–based computer program that allows rapid determination of %β and %S from measured values. This program is available free of charge for academic use from one of the authors (J.C.L.). Although the simple equations (3) give a qualitatively useful approximation of the model predictions, we recommend that HOMA calculations use the computer model in preference, in view of its more precise physiological basis and the validation data that are available and in the process of being published.

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References

1. van Haeften TW: Glucose tolerance, insulin sensitivity, and the homeostasis model assessment method (Letter). *Diabetes Care* 21:673, 1998
2. Matsumoto K, Yano M, Ueki Y, Miyake S: Response to van Haeften (Letter). *Diabetes Care* 21:673–674, 1998
3. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
4. Rudenski AS, Hosker JP, Burnett MA, Matthews DR, Turner RC: The β-cell glucose stimulus-response curve in normal humans assessed by insulin and C-peptide secretion rates. *Metabolism* 37:526–534, 1988
5. Rudenski AS, Matthews DR, Levy JC, Turner RC: Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism* 40:908–917, 1991
6. Hermans M, Coppack S, Levy J: Comparison of the efficiency of 4 *in vivo* insulin sensitivity tests to discriminate between individuals over the range of glucose tolerance by assessment of their discriminant ratio (Abstract). *Diabetes* 44 (Suppl. 1):200A, 1995
7. Hermans MP, Levy J, Coppack S, Shadid T, Turner RC: Comparison of the ability of 3 *in vivo* tests to discriminate differences in β-cell function over the range of glucose tolerance (Abstract). *Diabetologia* 38 (Suppl. 2):A30, 1995
8. Levy J, Manley S, Sutton P, Camps I: Beta-cell function assessed by the hyperglycaemic clamp: reproducibility compared with HOMA analysis from fasting values, and factors influencing variability (Abstract). *Diabetes* 44 (Suppl. 1):89A, 1995
9. Hammersley M, Levy J, Volpicelli G, Barrow B, Hatterlsey A, Turner R: Glucose tolerance and β-cell function assessed by continuous infusion of glucose and oral glucose tolerance test (Abstract). *Diabetologia* 35 (Suppl. 1):99A, 1992

Diabetic Instability and Celiac Disease

A frequent association to keep in mind

Celiac disease (CD) is caused by damage to differentiated villus epithelial cells in response to the ingestion of dietary gluten. The rate of IDDM and CD association is generally estimated to be 1–7% (1). Some clues suggest that these two conditions are linked by a common physiopathology. The first phase of insulin response is altered in islet cell antibody (ICA)-negative children with CD observed in the prediabetic state (2). In addition, some of these children with CD developed IDDM during a follow-up of 10 years (2). Furthermore, CD and IDDM are supported by an identical genetic background (class II HLA DR3 and HLA DQ2 genotypes) (1,3,4). Finally, similar mechanisms of β-cell and enterocyte cell damage mediated by tumor necrosis factor and γ-interferon are observed (4).

The recent routine accessibility of IgA endomysial antibody detection (the most sensitive and specific noninvasive screening test of CD) (1,5) showed that CD and IDDM are more frequently associated than previously reported. The usual symptoms of CD are diarrhea and a chronic malabsorption syndrome. Furthermore, the altered digestive absorption of meals worsened the metabolic control of diabetes, leading to diabetic instability. We report a case of poorly controlled IDDM caused by a severe CD free of any specific symptom.

A 47-year-old IDDM woman was referred for poor diabetic control. Her uncomplicated IDDM was diagnosed at 30 years of age. An intensive insulin therapy maintained diabetes near normoglycemia until 1 year before admission. In the last year, a loss of 1 kg of body weight (BMI 25 kg/m^2) was associated with frequent and unpredictable hypoglycemic or hyperglycemic periods. The daily calorie intake was unchanged, and no eating disorder was noted. Psychiatric pathology and factitious disease were excluded. The search for intercurrent illness was negative. Diarrhea was not present. Clinical examination was normal except for periumbilical subcutaneous lipodystrophies. Their exclusion as insulin injection sites did not improve metabolic parameters. No biological signs of malabsorption were found. Because of the presence of dyspeptic symptoms, we performed an upper digestive track fibroscopy that excluded diabetic gastroparesis. Systematic bowel biopsies showed complete mucosal atrophy typical of severe CD. IgA endomysial antibodies were positive (by indirect immunofluorescence assay). An improvement of metabolic control was observed 6 months after gluten-free diet introduction, and control bowel biopsies showed the disappearance of mucosal atrophy.

Our case was intriguing because of the lack of the usual biological and clinical features of CD. The disappearance of diabetic instability after the introduction of a specific gluten-free diet confirms the responsibility of CD in the bad metabolic control.

Diabetes instability is a severe disease that can endanger a patient's life. Because CD is a curable cause of bad metabolic control more often associated with IDDM than usually admitted, we suggest that all subjects with diabetic instability should be actively screened for CD, even if no spe-

cific digestive or biological symptoms are present. The use of the IgA endomysial antibody test seems to be of great use to facilitate the early diagnosis of CD in an asymptomatic IDDM population.

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References

1. Cronin CC, Shanahan F: Insulin dependent diabetes mellitus and coeliac disease. *Lancet* 349:1096–1097, 1997
2. Karagiozoglou-Lampoudi T, Nousia-Arvanitaki S, Augoustidou-Savopoulou P, Salem N, Polymenidis Z, Kanakouditsakalidou F: Insulin secretion decline unrelated to jejunal morphology or exocrine pancreatic function in children with celiac disease. *J Pediatr Endocrinol Metab* 9:585–591, 1996
3. Vardtal F, Johansen BH, Friede T, Thorpe CJ, Stevanovic S, Eriksen JE, Sletten K, Thorsby E, Rammensee HG, Sollid LM: The peptide binding motif of the disease associated HLA-DQ molecule. *Eur J Immunol* 26:2764–2772, 1996
4. Pena S, Garrote JA, Crusius JB: Advances in the immunogenetics of coeliac disease: clues for understanding the pathogenesis and disease heterogeneity. *Scand J Gastroenterol* 225 (Suppl.):56–58, 1998
5. Ferreira M, Davies SL, Butler M, Scott D, Clark M, Kumar P: Endomysial antibody: is it the best screening test for coeliac disease? *Gut* 33:1633–1637, 1992

Should Age and Sex Be Taken Into Account in the Determination of HbA_{1c} Reference Range?

In the last few years, a number of articles have shown the influence of aging on HbA_{1c} values in healthy populations (1–3). Because aging could be associated with weight gain, less exercise, increased drug intake, concomitant illnesses, etc., researchers have taken care to remove the influence of these factors on their studies and have confirmed that a physiological process exclusively linked to aging could be responsible for the increase in HbA_{1c} in older populations. Our aim, in a first study, was to confirm this increase in our population (Mediterranean area). We found that HbA_{1c} results were not related to sex, but they did show a clear increase with aging (4). More recently, we have carried out a broader study in a healthy population, selecting 540 men and 540 women with analytical results in the reference range. Individuals were classified into six age-groups: 20–29, 30–39, 40–49, 50–59, 60–69, and >70 years. Blood was collected in K3-EDTA tubes and stored at 4°C before the analysis. Determination of HbA_{1c} was performed using an HA-8140 high performance liquid chromatography system. The study confirmed (Table 1) the influence of aging in increasing the mean value of HbA_{1c}, but also allowed us to assess some differences related to the sex of the individuals. Effectively, despite the fact that the whole male and female populations did not show different mean HbA_{1c} values (men 4.84 ± 0.41%, women 4.81 ± 0.44%, $P = 0.298$), we found that young women exhibit lower values of HbA_{1c} (Fig. 1), though this difference is reduced with aging, and even higher values are observed in women >70 years of age, compared with men of the same age-group. These results, obtained in a Mediterranean population, agree with those found in a Chinese population and previously published (3).

Table 1—*HbA_{1c} mean differences*

	HbA_{1c} (%)	
	Women	Men
Age-group		
20–29	4.41 ± 0.26*†	4.58 ± 0.31*
30–39	4.56 ± 0.33*†	4.71 ± 0.40
40–49	4.68 ± 0.40*	4.79 ± 0.37*
50–59	4.95 ± 0.36*	4.88 ± 0.33
60–69	5.09 ± 0.31	5.08 ± 0.41
>70	5.17 ± 0.34†	5.01 ± 0.38

Data are means ± SD. $n = 90$ for all groups. *$P <$ 0.05 vs. group 1 decade older; †$P < 0.05$ vs. men.

Nowadays, the effect of aging in the interpretation of HbA_{1c} results could be limited by a number of factors that also affect the accuracy of this measurement. Among others, lack of international standardization is a challenge for the clinical interpretation of HbA_{1c} data because heterogeneity of results due to the use of different analytical techniques has still not been solved. However, if an international standardization for glycohemoglobin is finally reached, the influence of factors such as sex or aging could become clinically important in HbA_{1c} interpretation, and correction factors related to them could be necessary.

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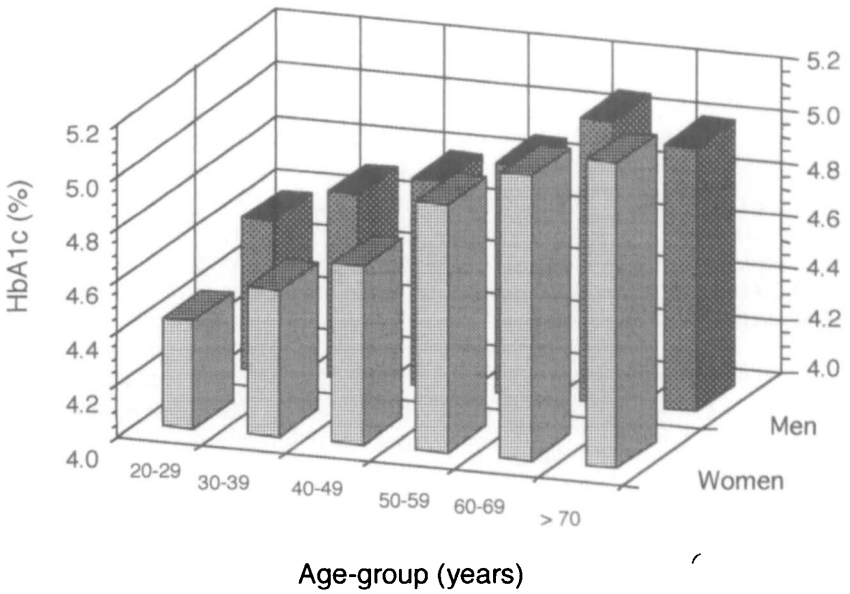

Figure 1—*Increase of HbA_{1c} mean value with aging.*