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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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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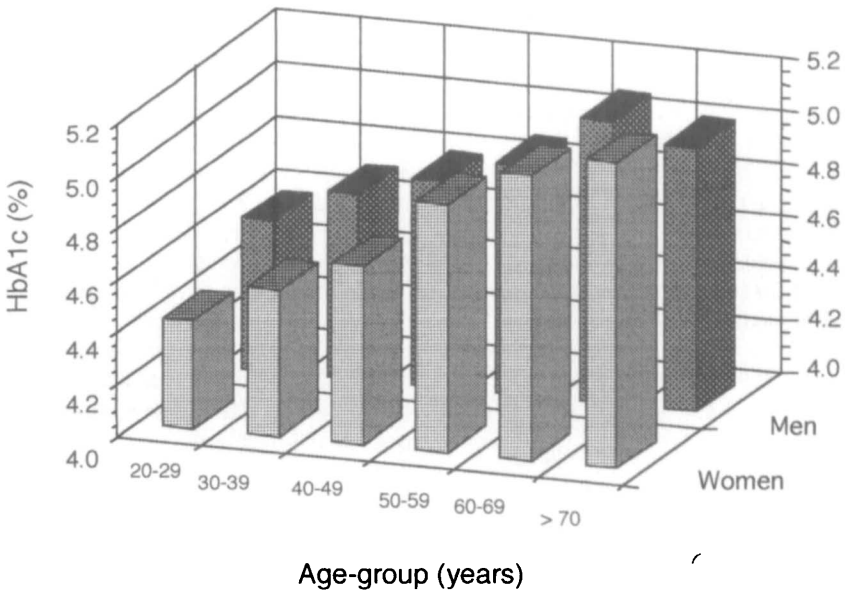

Figure 1—*Increase of HbA_{1c} mean value with aging.*

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Vanadyl Sulfate Does Not Enhance Insulin Action in Patients With Type 1 Diabetes

Vanadium, a transition metal found in trace concentrations in humans, has insulin-like effects in vitro (1–3) and in vivo (4,5). In vitro, vanadium stimulates glucose uptake and oxidation, and glycogen synthesis in adipocytes, skeletal muscle, and hepatocytes (6). In diabetic rats, large doses of vanadium improve glucose tolerance without an increase in plasma insulin (5) and cause an increase in hepatic glycogen (5,7,8). Thus, interest in vanadium as a possible treatment for diabetes has been intense.

In humans, we have demonstrated that low doses of vanadyl sulfate (VS) given for 3 weeks increased insulin-mediated glucose uptake, glycogen synthesis, and suppression of endogenous glucose production (EGP) in type 2 diabetic patients (9) but not in obese nondiabetic subjects (10). These improvements in hepatic and peripheral insulin sensitivity were associated with reduced lipid oxidation rates and plasma free fatty acid (FFA) concentrations. On the other hand, a recent study in type 1 diabetic patients given sodium metavanadate demonstrated a decrease in insulin requirements with no change in glucose metabolism (11). However, the relationship between the clinical findings of reduced insulin requirements and vanadium action per se is unclear. For example, the intracellular—and hence active—form of vanadium associated with an insulin-like effect is the vanadyl (V^{4+}) oxidation state of the element, as used in our previous studies, not vanadate (V^{5+}) (12,13). Thus, a plausible mechanism for vanadium action in type 1 diabetes remains unclear.

Because the effects of VS in type 2 diabetes may be to augment insulin action on lipolysis and EGP and both parameters are very sensitive to insulin in vivo, we used a low-dose insulin infusion to determine whether there is enhancement of insulin action, as seen in patients with type 2 diabetes. VS (100 mg/day) was given for 3 weeks and compared with 3 weeks of placebo in five type 1 diabetic subjects (age 31 ± 2 years; BMI 24 ± 1.6 kg/m^2). Plasma vanadium concentrations were 83.0 ± 29.4 μg/l after VS. There were no changes in insulin dose, weight, or appetite during the study period. While HbA_{1c} declined slightly, from 8.1 ± 0.4 to 7.6 ± 0.3%, serum fructosamine levels were unchanged (2.5 ± 0.1 mmol/l after both placebo and VS). Euglycemic-hyperinsulinemic clamps combined with 3-[^{3}H]glucose and constant specific activity were performed after each 3-week period. Glucose disposal was unchanged (26.37 ± 3.16 vs. 23.59 ± 3.89 μmol · kg^{-1} · min^{-1}, placebo vs. VS, respectively, NS). Similarly, glucose infusion rates needed to maintain euglycemia were unchanged (24.53 ± 3.28 vs. 21.59 ± 3.28 μmol · kg^{-1} · min^{-1}, NS). With indirect calorimetry, there were no significant changes in the whole-body oxidation rates of glucose or lipid. Finally, insulin-induced suppression of EGP (by ~70–80%) and plasma FFA (by ~50–60%) were comparable after placebo and VS.

Thus, a dose of VS previously determined to be well tolerated in humans and effective in patients with insulin-resistant type 2 diabetes did not enhance the effects of physiologic hyperinsulinemia on glucose and fat metabolism in type 1 diabetes. These results suggest that vanadium improves insulin action selectively in subjects with insulin resistance. While currently available, vanadium compounds remain as experimental probes to examine the mechanism of altered insulin action (14); more studies will be needed to establish any role for their clinical usage.

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