Vitamin D Deficiency Is More Common in Type 2 Than in Type 1 Diabetes

We report data from a pilot study examining vitamin D deficiency in type 1 and type 2 diabetes. Serum 25-OH vitamin D (25-OH-D) levels were measured in type 1 ($n = 50$) and type 2 diabetic ($n = 63$) individuals at the time of their routine visits for diabetes management. Patients had no prior history of metabolic bone disease, vitamin D deficiency, parathyroid disease, malabsorption, or significant elevations of serum creatinine or liver enzymes. Most subjects (74.3%) were prescribed a daily multivitamin as part of their routine diabetes care, but none were taking additional supplements. Serum was obtained during "light" (April to September) and "dark" (October to March) months. Serum 25-OH-D levels were measured using a competitive protein-binding assay (Esoterix, Calabasas Hills, CA). Vitamin D levels were classified as deficient (0–20 ng/ml) or expected (>20 ng/ml). Although 25-OH-D levels >32 ng/ml are optimal (1), levels ≥20 ng/ml are usually considered acceptable and are generally not treated in patients without metabolic bone disease.

Type 1 diabetic individuals were significantly younger than those with type 2 diabetes ([mean ± SE] 49.0 ± 1.7 vs. 61.2 ± 1.5 years, $P < 0.001$) and had a lower BMI (26.2 ± 0.7 vs. 33.9 ± 1.0 kg/m^2, $P < 0.001$). The majority (63.5%) of the type 2 diabetic individuals were deficient compared with 36% of the type 1 diabetic patients. The unadjusted mean 25-OH-D level for type 2 diabetic patients was 17.1 ± 1.2 ng/ml ($P < 0.05$) compared with 23.6 ± 1.2 ng/ml for type 1 diabetes ($P < 0.05$). Of the patients who were deficient, most were prescribed multivitamins (72.2% of type 2 diabetes, 72.5% of type 1 diabetes). Most patients having serum 25-OH-D levels >20 ng/ml were also prescribed multivitamins (73.9% of type 2 diabetes, 78.1% type 1 diabetes). Serum was obtained with equivalent distribution in light and dark months among both groups.

The 25-OH-D levels inversely correlated with BMI ($P < 0.01$) but were not directly related to age or sex. ANCOVA was used to compare 25-OH-D levels in type 1 and type 2 diabetic patients while adjusting for BMI and age. As was noted in the unadjusted levels, significantly lower 25-OH-D levels were found in type 2 relative to type 1 diabetic patients (mean adjusted 25-OH-D 18.1 ± 1.4 vs. 22.9 ± 1.6 ng/ml, $P < 0.001$). Among type 2 diabetic patients, mean 25-OH-D level was similar in those taking insulin compared with those on oral hypoglycemic agents (mean 25-OH-D 17.6 ± 1.6 and 16.8 ± 1.5 ng/ml, respectively; $P = 0.73$).

Our findings suggest that vitamin D deficiency is more common in type 2 diabetes than in type 1 diabetes, unrelated to age, sex, or insulin treatment. Although higher BMI was associated with lower 25-OH-D levels, the difference in vitamin D levels between type 2 and type 1 diabetic individuals persisted after adjusting for BMI. This difference may be therapeutically significant in that mean vitamin D levels in type 2 diabetic patients were in the deficient range whereas mean levels in the type 1 diabetic patients reached the expected level. Despite most type 2 diabetic patients being prescribed a daily multivitamin, usually containing 400 IU of vitamin D, the percent who were deficient remained unchanged. Further studies are needed to better understand the causes and clinical significance of the observed hypovitaminosis D and to investigate response to vitamin D replacement therapy.

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Reference

1. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R: Estimates of optimal vitamin D status. *Osteoporos Int* 16:713–716, 2005

Circulating Levels of Interleukin-18 Independent of Body Fat and Fat-Free Mass

Results from the MONICA/KORA study

Elevated systemic concentrations of interleukin (IL)-18, a potent proinflammatory cytokine, have recently been reported to increase the risk of developing type 2 diabetes in a prospective case-cohort study with a mean follow up of 10.8 years (1). IL-18 is secreted from adipocytes (2), and IL-18 levels were found to be increased in obesity and decreased after weight loss in obese women (3). However, we did not observe a direct relationship between BMI and IL-18 levels in a large population-based sample (1). Another recent study in 144 men surprisingly reported a significant association of IL-18 with fat-free mass (4). We now present a detailed analysis of the relationship of IL-18 serum concentrations with body composition and potential confounding effects by sex in 225 men and 230 women from the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease)/KORA (Cooperative Health Research in the Region of Augsburg) Survey 1994/1995 (1), for whom bioelectric impedance data were available.

Serum IL-18 concentrations did not differ between men and women (geometric means 154.4 and 163.9 pg/ml, respectively; $P = 0.38$). For men and women combined, log IL-18 was not significantly correlated (Pearson) with absolute fat mass ($r = -0.02$; $P = 0.58$), percent fat mass ($r = 0.01$; $P = 0.82$), and fat-free mass ($r = -0.04$; $P = 0.38$). Separate analyses for men and women yielded similar results. The strongest correlations were seen between log IL-18 and systolic blood pressure ($r = 0.11$; $P = 0.01$), diastolic blood pressure ($r = 0.11$; $P = 0.01$), log C-reactive protein ($r = 0.09$; $P = 0.054$), and log IL-6 ($r = 0.10$; $P = 0.02$), whereas correlations with BMI, waist circumference, cholesterol levels, and uric acid did not reach statistical significance.

Taken together, these data show that systemic IL-18 concentrations are independent from body fat composition in-

cluding fat-free mass and support the hypothesis that adipose tissue is not a major contributor to circulating IL-18. This is not in contrast with data on IL-18 expression in adipocytes, since the reported amount of in vitro secreted IL-18 was rather low (2). This finding does not preclude a role for adipocyte-expressed IL-18 in adipose tissue since higher concentrations, which are relevant for the cross-talk between adipocytes and infiltrating immune cells, might be reached locally. Furthermore, we did not find a sex difference in the relation between IL-18 and markers of body fat composition, whereas this has been demonstrated for C-reactive protein and other inflammatory mediators (5). We conclude that the reported impact of weight loss on IL-18 levels (3) is indirect, as long-term caloric restriction (3) can be assumed to attenuate systemic immune activation and therefore also reduce IL-18 in the circulation. On the other hand, extensive weight loss is associated with a substantial increase in insulin sensitivity. The data linking increased IL-18 with reduced insulin sensitivity (4) and elevated type 2 diabetes risk (1) indicate that insulin resistance and not obesity per se may be the major determinant of circulating IL-18 concentrations.

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References

1. Thorand B, Kolb H, Baumert J, Koenig W, Chambless L, Meisinger C, Illig T, Martin S, Herder C: Elevated levels of interleukin-18 predict the development of type 2 diabetes: results from the MONICA/KORA Augsburg Study, 1984–2002. *Diabetes* 54:2932–2938, 2005
2. Skurk T, Kolb H, Müller-Scholze S, Röhrig K, Hauner H, Herder C: The proatherogenic cytokine interleukin-18 is secreted by human adipocytes. *Eur J Endocrinol* 152:871–876, 2005
3. Esposito K, Pontillo A, Ciotola M, Di Palo C, Grella E, Nicoletti G, Giugliano D: Weight loss reduces interleukin-18 levels in obese women. *J Clin Endocrinol Metab* 87:3864–3866, 2002
4. Bosch M, Lopez-Bermejo A, Vendrell J, Musri M, Ricart W, Fernandez-Real JM: Circulating IL-18 concentration is associated with insulin sensitivity and glucose tolerance through increased fat-free mass. *Diabetologia* 48:1841–1843, 2005
5. Thorand B, Baumert J, Döring A, Herder C, Kolb H, Rathmann W, Giani G, Koenig W, the KORA Group: Sex differences in the relation of body composition to markers of inflammation. *Atherosclerosis* 2005 [Epub ahead of print]

COMMENTS AND RESPONSES

The Metabolic Syndrome: Time for a Critical Appraisal: Joint Statement From the American Diabetes Association and the European Association for the Study of Diabetes

Response to Kahn et al.

We read with interest the American Diabetes Association statement about the metabolic syndrome (1). The idea that the aggregation of borderline risk factors could result in cardiovascular damage equal or superior to that occurring in individuals carrying a full-weight risk factor disease was intriguing. However, this intuition was soon polluted by inclusion of patients with frank diseases. If the philosophy of the metabolic syndrome is to draw firm attention upon "at very high risk" subjects, then the time has come to capture only subjects falling into borderline categorical zones using the Adult Treatment Panel III criteria: fasting glucose levels between 110 and 126 mg/dl, triglycerides between 150 and 200 mg/dl, HDL cholesterol between 30 and 40 mg/dl for men and between 40 and 50 mg/dl for women, blood pressure between 130/80 and 140/90 mmHg, and similar waist circumference values in the absence of obesity (BMI >30 kg/m^2). If, however, the basilar concept is the construct of an algebraic hierarchy of risk, the reflections of Kahn et al. (1) claim for the noninferiority of the sum of components versus the whole syndrome. The concept of a "pure" metabolic syndrome, i.e., identifying subjects without frank diseases such as diabetes, obesity, atherogenetic dyslipidemia, and hypertension, would have some benefits: *1*) to avoid double-labeled diagnosis, for example diabetes and the metabolic syndrome; *2*) to give the real number of subjects at risk and to trace the natural history of the syndrome; and *3*) to interfere with its evolution with lifestyle or pharmacological interventions. In the National Health and Nutrition Examination Surveys III sample, ~8% of coronary heart disease events occurred in people with only borderline levels of multiple risk (2). Moreover, intensive lifestyle intervention (3), diet (4), and drugs (5) have all been shown to be effective in reducing the prevalence of metabolic syndrome, although interventions based on diet, physical activity, and weight reduction seem to work better than drugs. Lastly, it would be easier to force a labeled patient (that with a pure syndrome) to follow advice for lifestyle changes than for unlabeled subjects with one or more borderline risk factors. Since the way to disseminate healthy practices is all but easy, any help is welcome.

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References

1. Kahn R, Buse J, Ferrannini E, Stern M: The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 28:2289–2304, 2005
2. Vasan RS, Sullivan ML, Wilson PWF, Sempos CT, Sundstrom J, Kannel WB,