The American Diabetes Association's 57th Annual Advanced Postgraduate Course

Diabetes risk, vitamin D, polycystic ovary syndrome, and obstructive sleep apnea

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Risk prediction in diabetes

Michael Stern (San Antonio, TX) discussed risk prediction in diabetes, addressing the use of biomarkers and approaches with risk calculation engines. In general, he noted, the state of wellness is inherently asymptomatic without functional impairments, and many individual with diagnosed diabetes, hypertension, and even with cardiovascular disease (CVD) are "well." For these individuals, treatment provides no current benefit but only the promise of a future benefit, which may never come to pass. If a well person in this sense cannot be made better, Stern pointed out that we must be particularly cognizant of the dictum ascribed to Niels Bohr: "Prediction is very difficult, especially about the future."

A tool used in analysis of tests is the calculation of the area under the curve (AUC) of the receiver-operating characteristic graph of sensitivity versus (1-specificity). The AUC can be interpreted to equal the likelihood that a person destined to develop the disease or characteristic being tested for has a higher score, comparing one person who is with another who is not going to develop the given outcome (1). The AUC should be contrasted with an odds ratio (OR) or relative risk, which may be calculated as equaling (sensitivity) × (1 − false positive rate)/[(1 − sensitivity) × (false positive rate)]. This may better be thought of as pertaining to populations, with an OR of 1.5–3.0 giving rise to AUCs of 0.57–0.68, which Stern termed not terribly impressive levels, as can be observed in the overlap of distribution curves of those developing versus not developing the disease or characteristic. An OR of 10 is needed to give a reasonable AUC of 0.83 and, hence, to distinguish individuals, whereas an OR of 1.5 is useful in distinguishing populations.

Stern reviewed the San Antonio study diabetes prediction model, which is based on age, sex, ethnicity, fasting glucose, systolic blood pressure, BMI, and family history (2). The AUC is 0.85 for this model, a level higher than that seen with the fasting or the 2-h postglucose load blood glucose alone. Stern commented also that impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are given as fixed points, while this (or any) predictive equation gives a range of values whose cut point can be set at whatever level seems appropriate for a given population. A recently proposed approach is the commercially available Tethys assay, which gives a diabetes risk score (DRS) using fasting glucose, 2-h insulin, adiponectin, ferritin, interleukin-2 receptor α, C-reactive protein, and, in some applications, A1C. The DRS has been validated based on the Inter99 study of 6,794 Danes (3) and the Botnia study of 1968 Finnish and Swedish subjects (4), with 5- and 15-year follow-up, respectively. The score ranges from 1–10 and low risk is considered <4.5, moderate 4.5–8, and high >8. Stern illustrated the use of the DRS by reviewing its contribution to risk assessment in those with IFG, whose 9% risk of developing diabetes exceeds by up to 2% the risk of those with NFG. Among the IFG group, those with low DRS (comprising 26% of the group) have 2% risk, those with moderate risk (53%) have 7%, and the 21% with high-risk DRS scores have 24% risk of converting to diabetes over 5 years, suggesting that clinically useful additional information can be gained from this approach (3). In a similar analysis, the 25% of the population with metabolic syndrome had an overall 8% risk, while those remaining had 2% risk of developing diabetes. Stratifying those with metabolic syndrome, the 23% with low DRS had 2% diabetes risk, the 54% with moderate DRS had 6% diabetes risk, and the 23% with high DRS developed diabetes at a 23% rate. Thus, risk models are more potent than dichotomous measures such as IFG and metabolic syndrome and, hence, "contain more information about the future." The AUC for the DRS is similar to that of the Stern risk model at a bit over 0.8, suggesting that a clinical score (inexpensive, in the sense that ascertainment of data by clinicians is considered to be "free") would have similar benefit to the Tethys test.

Why, Stern asked, should we bother with risk prediction scores? How is the information to be used? Certainly, one can more aggressively treat blood pressure and lipids, but he commented, "you don't really need a diabetes risk score" for this. The reason, rather, is precisely to prevent diabetes and, more importantly, by doing so to prevent its complications. "We know that we can prevent diabetes," as the Finnish Diabetes Prevention Study, the Da Qing Diabetes Study, the Diabetes prevention program, Tripod, DREAM, and Act-Now have shown. "I am of the opinion," Stern continued, "that we really need studies that show an impact on hard end points." Surrogate measures such as glucose, blood pressure, coronary Ca^{++}, and carotid IMT "can have abnormal values [while the person is] 'well.'" Actual morbidities to be prevented are death, heart attack, stroke, end-stage renal dis-

ease, blindness, and amputation, and Stern said, "I reserve the right to remain skeptical." It is, he said, possible that waiting for diabetes to develop might be adequate if aggressive treatment measures are then employed. The long-term Diabetes Prevention Program (DPP) Outcomes Study is under way (5), he added, and "whether or not it will give definitive information we shall see."

A related issue is whether screening should be done to identify diabetes itself at an earlier stage. Again, Stern said, we need to demonstrate benefits of early as opposed to delayed treatment. The conservative approach would be to wait until diabetes presents, more aggressive would be to screen, and most aggressive would be to predict. ADA Position Statements in the past have suggested that screening begin at age 45 years and be carried out every 3 years, particularly for those with BMI $\geq$25 kg/m^2 (6), but Stern wryly observed that such recommendations are "not exactly data driven," and the current ADA guidelines, although discussing the approach to the person who is found to have "pre-diabetes," are silent on how such ascertainment should be carried out (7). The U.S. Preventive Services Task Force recommends screening for individuals with blood pressure >135/80 mmHg, as treatment recommendations are different if diabetes is present, but Stern noted that this, too, is not data driven. Using the Archimedes Model, a simulation study compared health outcomes with eight different diabetes screening strategies, starting at age 30 years every 3 years; at age 45 years every 1, 3, and 5 years; at age 60 years every 3 years, at the time of hypertension diagnosis, just once, or every five visits; or, the maximal strategy, beginning at age 30 years and then repeating every 6 months. In all cases, treatment to achieve recommended glucose, blood pressure, and lipid levels, taking into account known information about compliance, was used in predicting outcome (8). Without screening, diabetes was present in ~15% of individuals at age 56 years, 20% at age 67 years, and so on. All the strategies prevented 2–5 deaths per 1,000 people (of ~250 deaths per 1,000 individuals), prevented 3–9 myocardial infarctions of ~150, and prevented 3–9 microvascular complications of 120, with little effect on stroke. "The effects of this are modest," Stern concluded, "let's face it," although the study did find that screening for type 2 diabetes is cost-effective when started

between ages 30–45 years and repeated every 3–5 years, at a cost of $10,000–15,000 per quality-adjusted life year (QALY); most cost-effective was screening hypertensive individuals annually, at $6,287/QALY.

Vitamin D and diabetes
Neil Binkley (Madison, WI) discussed vitamin D, whose deficiency may contribute to the pathogenesis, prevention, and treatment of diabetes. A serum 25-hydroxyvitamin (25-OH) D level of ~40 ng/ml appears appropriate but requires ingestion of 2000–4,000 IU daily. Vitamin D is produced from 7-dehydrocholesterol, which forms pre-D3 on exposure to ultraviolet light; Binkley noted that few foods have vitamin D, with cod liver oil having 1,360 IU vitamin D per tablespoon but also containing huge amounts of vitamin A, which can cause bone loss, making this not a useful approach. Rickets was first described by Whistler in the 1600s in England, and by the late 1800s it affected a substantial number of children in Europe. The discovery that radiation of food cured rickets led to elimination of the disease in the U.S., although it does occur in breast-fed infants, particularly of vitamin D–deficient African American women. Few foods, however, are sufficiently fortified to achieve currently recommended 25-OH D levels, for which one would need to drink 10–40 glasses of milk daily (9). "We're indoors," Binkley said, "we wear sunscreen, we wear clothes . . . with advancing age our skin becomes less able to make vitamin D." There is progressive worsening of vitamin D status with age (10) and with increasing degrees of obesity (11), leading Binkley to speculate as to whether vitamin D deficiency might be a cause rather than a consequence of increased body weight.

25-OH D may be considered the storage form of the vitamin, with circulating levels of 1,25 regulated. Vitamin D deficiency upregulates parathyroid hormone (PTH), increasing renal 1α-hydroxylation of vitamin D, so 1,25 di-hydroxy-vitamin D measurement is only useful in individuals with renal disease. Vitamin D deficiency is considered to occur with 25-OH D levels <10. Sufficiency is considered by U.S. groups to require levels >30 ng/ml (12), although Binkley pointed out that the European recommendation is for levels >20 ng/ml. Based on the relationship between vitamin D and PTH as a marker of bone health, it may be that the opti-

mal 25-OH D varies by system, with optimal levels for bone and skeletal muscle 38–40, while periodontal and cancer prevention requirements may be lower (13). The Institute of Medicine Food and Nutrition Board is currently reviewing dietary reference intakes for vitamin D, and Binkley suggested that they probably will recommend 800–1,000 IU/day, which Binkley termed "conservative," noting that to achieve levels >30 ng/ml for 97.5% of individuals a daily intake of 2,600 IU is required (14). Both forms of the vitamin, D3 and D2, are effective, and in the U.S. the high-dose 50,000 unit prescription tablets are only available as D2. Both forms appear to be similar in curing Rickets in older studies (15), but vitamin D2 has shorter duration of activity (16) and vitamin D3 may be slightly more potent (17). Binkley reviewed his studies showing that 25-OH D measurement is very laboratory specific (18), although the measurement has improved and reference materials are now available, but he recommended, "if you're aiming to be above 30 ng/ml, aim for 40." The test is rather expensive, costing >$100, a prohibitive >$30 billion expense if done on all Americans. He recommended its measurement in patients with osteoporosis, increased risk of falling, malabsorption, and perhaps those with malignancies and those with diabetes.

Binkley stated that vitamin D levels >30 ng/ml are safe, with no effect on serum or 24-h urine calcium (19–21). Vitamin D intoxication, Binkley said, requires ingestion of >10,000, and perhaps >40,000 units daily, with each additional 1,000 units increasing circulating 25-OH D by ~6 ng/ml (22). The usual 25-OH D level in individuals intensely exposed to sunlight is 60–80 ng/ml (23). This shows considerable variability, with Binkley describing a study of surfers in Hawaii whose 25-OH D ranged from 10 to 65 ng/ml. Particularly lower levels were seen in those of Asian ethnicity. Given this variability, one should be careful in recommending replacement doses. Binkley suggested that individuals with screening levels 30–40 ng/ml should have a daily 1,000 IU supplement that at 20–30 ng/ml a 2,000 IU supplement be used, and that those with levels <20 ng/ml receive a prescription dose of 50,000 IU weekly for 8 weeks or 50,000 IU three times weekly for 4 weeks. Food fortification might be an effective population approach, but

there is currently no evidence to support this. It is noteworthy that intracellular 1α-hydroxylation of vitamin D occurs in many tissues (24), leading to a variety of autocrine/paracrine nonclassical effects. Higher levels of vitamin D are associated with lower risks of malignancy (25), and vitamin D appears both to improve β-cell function and insulin action (26). Numerous epidemiologic studies show association of low vitamin D levels and of lack of supplementation with higher rates of development of diabetes (27–30). The dose used is important, with no benefit found from administration of calcium plus 400 IU vitamin D daily in the Womens' Health Initiative (31) or with an 800 IU daily dose in RECORD (32).

Fascinating studies show that at latitudes near the equator type 1 diabetes incidence is lower (33), and Finn children supplemented as infants had much lower type 1 diabetes risk, while those who developed rickets had higher risk (34,35). There is also evidence that vitamin D reduces risk of macular degeneration (36), of development of renal disease both in animal models (37) and in human population studies (38), of myocardial infarction (39), and of mortality (40), although Binkley cautioned that low vitamin D status may be a surrogate for illness or socioeconomic factors, which could explain the epidemiologic associations.

Cardiometabolic risk and polycystic ovary syndrome

Andrea Dunaif (Chicago, IL) noted that the major factors giving rise to polycystic ovary syndrome (PCOS) are metabolic, in association with insulin resistance and obesity, with the consequent development of hyperandrogenemia and anovulation affecting 7% of premenopausal women. An additional 5–20% of premenopausal women have hyperandrogenemia, which increases with obesity and may contribute to premenopausal cardiovascular risk. PCOS is present in 25% of type 2 diabetic women, while anovulation and high androgen levels identify women at particular risk of developing diabetes. The risk of type 2 diabetes increases among adolescent and young adult women with PCOS (41), with obesity further increasing risks of diabetes and of hypertriglyceridemia (42). Ovarian function abnormality is, then, necessary for the diagnosis of PCOS. It is noteworthy that longer menstrual cycle length is associated with diabetes risk (43). Insulin resistance is seen in lean as

well as in obese women with PCOS (44), with thiazolidinedione administration improving this (45). PCOS, obesity, and cardiometabolic risk factors are, Dunaif pointed out, closely correlated, and she noted that testosterone also worsens these factors and that administration of the antiandrogen flutamide was shown to reduce visceral fat and increase insulin sensitivity (46).

PCOS has a strong genetic component, Dunaif stated, having high correlation ($r = 0.71$) in monozygotic twins. She noted that 40% of sisters of women with PCOS have features of the syndrome and elevated testosterone, with brothers of women with PCOS having elevated dehydroepiandrosterone levels (47). Metabolic syndrome aggregates in families of women with PCOS (48,49), while in animal models prenatal androgen administration produces a metabolic syndrome phenotype (50).

Coronary artery calcium levels are increased in PCOS (51), although it is noteworthy that women with hyperandrogenemia but normal ovaries and ovulation do not appear to have increased cardovascular risk and not all epidemiologic studies have shown increased coronary artery disease risk in young women with the syndrome (52). Irregular menses are, however, associated with higher cardiovascular risk (53), and there is evidence of increased mortality among women with PCOS (54). An important therapeutic question is whether oral contraceptives have adverse metabolic consequences. There may be adverse effect of such agents containing cyproterone, but no adverse effect has been seen with low-dose estrogen preparations (55) or with the very commonly used preparation ethenyl estradiol/drosipirenone, which may nave antiandrogenic effects (56). Metformin (57) appears to have cardiovascular as well as metabolic benefit in PCOS, and interestingly, there is evidence of endocrine as well as lipid benefit of simvastatin in the condition (58).

Obstructive sleep apnea and diabetes

Esra Tasali (Chicago, IL) discussed associations between obstructive sleep apnea (OSA) and type 2 diabetes. OSA is a condition of recurrent collapse of the upper airway during sleep, resulting in reductions in oxygen staturation and transient arousal, typically not remembered by the individual. OSA is associated with obesity, particularly central; age; male sex;

and the phenotype of enlarged tongue, soft palate, uvula, and tonsils, with increased neck circumference, reducing the upper-airway cross-sectional area. Alcohol and sedative and antihistamine use are additional causes. The condition may not be associated with specific nocturnal symptoms or may be associated with nocturnal snoring, choking, restlessness, sweating, and esophageal reflux, and because of the recurrent arousal may be a common cause of nocturia. The diagnosis is by sleep study with polysomnography, with the apnea/hypopnea index the number of such episodes occurring hourly during sleep; <5 is normal, and 5–14, 14–29, and ≥30 are considered to represent mild, moderate, and severe OSA, respectively. The treatment most often recommended is continuous positive airway pressure (CPAP), which acts as a splint to prevent upper-airway collapse, but despite the development of various face masks and nasal cannulae and devices that are smaller, humidified, and quieter, compliance with use of this treatment is poor, with patients on average using CPAP less than half of the time recommended. Oral appliances to bring the jaw forward are helpful.

There is evidence that OSA is linked to CVD and diabetes, in part indirectly from the association of obesity, hypertension, cigarette use, and other cardiovascular risk factors with OSA as well, but there is evidence that OSA is related to insulin resistance and diabetes risk. The prevalence of OSA in type 2 diabetic individuals has variously been reported at 58% (59), 71% (60), and 86% (61). Furthermore, the degree of severity of OSA is, in patients with diabetes, associated with the A1C level (62). Interestingly, one of the mechanisms of the association of PCOS with insulin resistance may involve OSA (63). Conceptually, both fragmentation of sleep and the intermittent hypoxemia caused by OSA may lead to increased sympathetic activity, activation of the hypothalamic-pituitary-adrenal axis, and the elaboration of proinflammatory cytokines from adipocytes and other cell types. If OSA causes diabetes and, in diabetic individuals, increases the blood glucose, Tasali asked, might treatment of OSA improve glycemia? A study of 25 diabetic individuals showed CPAP to reduce A1C and, on continuous glucose monitoring, postprandial glycemia (64). Few prospective or interventional studies have been carried out, however, and many other studies have had negative re-

sults, although this may represent small sample sizes and poor compliance with CPAP, with those studies reporting this measure suggesting fewer than half of the expected hours of use of the devices.

Tasali reviewed several studies that she has carried out. In an experimental model of OSA in which healthy volunteers were aroused with loud noises when they entered deep (stage 4) sleep, leading to unchanged total sleep duration, insulin sensitivity decreased 25%, with spectral analysis of heart rate variability suggesting increased sympathetic tone. A 5-day period of sleep deprivation caused abnormal glucose tolerance with decreased insulin secretion. Interestingly, there is evidence that sleep deprivation increases measures of inflammation. Comparing 22 individuals with habitual short sleep times (averaging 5.25 h) with 22 normal sleepers (averaging 7.8 h nightly), glucose tolerance was normal but with increased insulin secretion, suggesting insulin resistance. Sleep deprivation may alter appetite regulation, reducing levels of leptin and increasing ghrelin and leading to increased appetite, with increases in self-reported appetite and in preference for carbohydrate in such a setting (65). Sleep loss, then, may contribute to the development of diabetes, Tasali suggested. Furthermore, a vicious cycle might occur in individuals with established diabetes of OSA leading to hyperglycemia, requiring increasing glucose-lowering treatment, which could in turn cause weight gain and worsen the sleep apnea. Given this perspective, she remarked upon the weight gain in the intensive glycemic treatment group of the Action to Control Cardiovascular Risk in Diabetes (AC-CORD) study and suggested that a component of their increased mortality might be related to unrecognized development of OSA.

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