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EDITORIAL

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Tweeting, tweeting

It is a useful exercise in brevity to limit one's thoughts to 280 characters and an image. I've been "tweeting" for more than a decade, and in 2018 used tweets for the basis of an American Diabetes Association meeting report.[1] In the era of COVID-19, we are moving to virtual patient visits and virtual meetings, and online forums have the potential to enrich our understanding of diabetes. Here's a look over my 2020 Twitter notes.

In the present issue of the *Journal of Diabetes*, Jing et al show that low bone mineral density in 482 men with type 2 diabetes tracked with low estradiol and high follicle-stimulating hormone, without effect of testosterone or sex hormone-binding globulin. This implies an important role of metabolism and sex hormone changes in bone homeostasis among people with diabetes.[2] Clinical questions about nonalcoholic fatty liver disease (NAFLD) abound. One is whether incidentally discovered NAFLD on imaging has the same consequence as NAFLD associated with elevations in liver function tests. In a report of a ≥7-year follow-up of imaging and alanine aminotransferase (ALT) measurements from 130 US Veteran's Administration hospitals from 2004 to 2008, 15 419 patients had NAFLD and elevated ALT, and 9267 patients had neither NAFLD nor elevated ALT; the former group had approximately 4-fold greater likelihood of developing cirrhosis. An additional 3522 patients had NAFLD and normal ALT, and showed no significant increase in cirrhosis.[3] A series of publications in *Diabetologia* in 2009 raised concern that insulin glargine was associated with increased likelihood of cancer risk, although the data never seemed sturdy enough to avoid use of this important basal insulin preparation.[4-6] Now a dataset study of more than 300 000 insulin-treated women initiating treatment with glargine, detemir, or neutral protamine Hagedorn (NPH) insulin appears to have permanently put to rest the notion that insulin glargine might have an association with breast cancer.[7]

Precision management of type 2 diabetes now may include the use of genetic information. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial participants with the haptoglobin (Hp) 2-2 genotype had reduction in atherosclerotic cardiovascular disease endpoints with intensive glycemic treatment, while Hp 1-1 and Hp 1-2 not only were associated with lack of CVD benefit but also with increased mortality when subjected to intensive treatment.[8] Another genotype/phenotype analysis of ACCORD showed that the T/T PPARα genotype was associated with nearly a halving of major adverse cardiac events (MACEs) with fenofibrate treatment. This is a CVD outcome benefit similar to that seen in participants both with high-density lipoprotein cholesterol <35 and triglyceride >203 mg/dL.[9] Another potentially important genetic heterogeneity affecting sodium glucose cotransporter 2 inhibitor (SGLT2i) response, although not readily ascertained in clinical management: Variable expression of alpha cell SGLT2 RNA and protein appears to track with variation in dapagliflozin-induced in vitro glucagon secretion from 31 islet donors.[10]

Recent population studies showed an additive effect of chronic kidney disease (CKD) and diabetes on post-myocardial infarction mortality,[11] and an additive effect of diabetes and hypertension control both on albuminuria and on left ventricular hypertrophy, to an extent similar to that reported in ACCORD and other trials.[12] A trial of hypertension treatment at mean age 81 showed that reducing systolic pressure to 128 vs 144 improved brain change on MRI, as well as being associated with reduction in CVD outcome, supporting a systolic blood pressure goal of 130 regardless of age.[13] What antihypertensive treatment is used is however important. Among more than 700 000 hypertensive persons treated with chlorthalidone or hydrochlorothiazide, CVD risk was similar, but there was greater likelihood of harm with the former agent, which was associated with greater likelihood of type 2 diabetes, acute renal failure, CKD, hypokalemia, hypomagnesemia, and hyponatremia, and also with hyperkalemia, anaphylactoid reactions, and gout.[14] A study of hypomagnesemia showed it to be associated with increased CVD mortality among more than 3000 persons with CVD followed for >7 years.[15] A recent subgroup analysis of the dapagliflozin cardiovascular outcome trial (DECLARE-TIMI58) showed that with a diabetes duration of >20 years, the agent not only reduced heart failure but also MACEs and all MACE components.[16] In a report on 3909 ACEI/ARB (angiotensin-converting enzyme inhibitor/angiotensin receptor

blocker)-treated persons whose estimated glomerular filtration rate decreased to <30 mL/min, 1235 discontinued the treatment within 6 months while 2674 did not. Over nearly 3 years, propensity score-matched mortality and MACE risk increased 39% and 37% in those stopping ACEI/ARB treatment.[17] At the beginning of the natural history of diabetes, a meta-analysis showed reduction in risk of diabetes development in randomized controlled trials with ACEIs, and a Mendelian randomization analysis showed association of genetically lower serum ACE levels with lower diabetes risk, perhaps in part mediated by lower body weight with lower ACE level.[18] One wonders whether measurement of circulating ACE levels would allow greater precision in determining persons appropriate for ACEI/ARB treatment.

Two other noteworthy reports: Analysis of >17 000 diabetic ketoacidosis hospitalizations in Australia and New Zealand showed serum osmolarity to have a greater effect than the degree of acidosis in predicting adverse outcome.[19] Neuropathic pain is a major issue in clinical management, but an issue is the potential of pharmacologic management to have significant side effects, including sedation and weight gain. We have reviewed studies showing benefit of acupuncture,[20] and the recent publication of a trial comparing real with sham acupuncture found an impressive halving of neuropathic pain with the former.[21]

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