CLOSER LOOK

WCPD 2016 (World Congress on the Prevention of Diabetes and its Complications)

December 2-4, 2016; Atlanta, GA; Days #1-2; Highlights - Draft

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Our team spent the first weekend of December in Atlanta, GA for the ninth World Congress on the Prevention of Diabetes and its Complications (WCPD 2016). Wow was this a great meeting! Speakers from around the world shared their perspectives on prevention, discussing type 2 diabetes, prediabetes, and obesity in intimate, interactive sessions - and, there was even a session on type 1 diabetes prevention. With so much learning packed in, it was hard to pick highlights, but we bring you our top takeaways from days #1-2 of the meeting below!

You can also read our conference preview for all the goings-on at WCPD 2016. We'll be back in a moment with highlights from day #3.

Top Eleven Highlights

1. Among the many arguments we heard in support of metformin as a prediabetes intervention, Dr. John Buse presented one of the strongest with a compelling economic and evidence-based case for metformin as a population-level prevention strategy. He's a complete powerhouse and we'd love him to be Diabetes Czar.

2. Dr. Simon Heller of the International Hypoglycemia Study Group made the case for a revised definition of hypoglycemia. He advocated that hypoglycemia needs to be measured in more depth and proposed a third prong in between <70 mg/dl as an "alert value" and <40 mg/dl as a sign of severe impairment requiring external assistance - <54 mg/dl would be added as an indication of clinically-relevant, severe hypoglycemia, creating a more comprehensive schematic of hypoglycemia in clinical trials and diabetes care. There remains a lack of clarity here in terms of understanding "real life" and "clinical" perspectives ("so, if I'm walking around with 55 mg/dL all day, this new system means I'm okay?"). Notably, there has been some grumbling in various quarters that there was no patient representation on this important committee and very little gender and ethnic diversity.

3. In a highly-anticipated WCPD tradition, Dr. Abraham Thomas presented a rapid-fire overview of the very latest clinical trial results in the field of diabetes prevention.

4. University of Illinois at Chicago's Dr. Ben Gerber presented a skeptical view of mobile health solutions, pointing to the mixed evidence on effectiveness and the lack of empirical evidence on health outcomes (such as CV events). We wait better data, particularly impacting adherence, especially as less data has to be manually input. Notably, he maintained an optimistic opinion on the potential for mobile health strategies to enhance diabetes prevention and care, but suggested that we still have a ways to go in identifying optimal evidence-based approaches.

5. "A person with diabetes engages with her healthcare team only 0.007% of the time - that's even less for someone with prediabetes." Emphasizing that a majority of diabetes management is self-*management, immediate past AADE president Dr. Deborah Greenwood presented social media as a powerful tool for the diabetes community. Dr. Greenwood also highlighted ongoing work with the International Diabetes Online Community Research Council (iDOCr), and we look forward to following the council's work investigating research questions to optimize social networking conversations.*

6. Dr. Paolo Pozzilli (University Campus Bio-Medico, Rome, Italy) provided an update on prevention efforts for type 1 diabetes at the primary and secondary levels.

7. In an engaging debate on the use of SGLT-2 inhibitors in type 1 diabetes, Dr. Kathleen Wyne pointed to the profound weight loss, decrease in blood pressure, and opportunity to educate patients on euglycemic DKA (arguing pro) while Dr. Mick Kumwenda underscored the DKA risks and lack of sufficient evidence on SGLT-2 inhibitors in type 1 patients (arguing against).

8. A lively symposium on nutrition convincingly demonstrated the value of dieting in a macronutrient-selective (rather than macronutrient-eliminating) manner.

9. Dr. Timothy Garvey (University of Alabama, Birmingham, AL) made the powerful argument that effective diabetes prevention must be grounded in meaningful efforts for obesity prevention.

10. Ms. Martha Funnell discussed some of the major behavioral challenges relevant to diabetes care and presented strategies to boost patient engagement.

11. Establishing a framework for the meeting, a workshop on the AACE prediabetes and obesity treatment algorithms discussed the multiple meanings of "prevention."

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Top Eleven Highlights

1. Among the many arguments we heard in support of metformin as a prediabetes intervention, Dr. John Buse presented one of the strongest with a compelling economic and evidence-based case for metformin as a population-level prevention strategy. Dr. Buse (University of North Carolina, Chapel Hill, NC) reviewed a number of prevention studies - including the ORIGIN trial investigating insulin glargine (Sanofi's Lantus), the SEQUEL trial investigating phentermine/topiramate extended-release (Vivus' Qsymia), the SCALE program investigating high-dose liraglutide (Novo Nordisk's Saxenda), and the EDIT and Diabetes Prevention Program (DPP) trials investigating metformin - ultimately concluding that metformin should be considered as a first line of defense in people with prediabetes. Dr. Buse underscored that "Saxenda is definitely effective" in stimulating weight loss and delaying type 2 diabetes, but turned to economics to show why metformin is the most reasonable approach to prediabetes. It would cost a little over $4 billion to treat the entire US prediabetes population with metformin vs. >$1.2 trillion to treat this group with liraglutide. Meanwhile, we learned in a separate session that intensive lifestyle intervention as provided by the DPP costs ~$100/person/session - treating 86 million Americans with prediabetes would thus run a bill of ~$1.4 trillion. These numbers make it hard to argue against metformin as a population-level solution for type 2 diabetes prevention (although on an individual basis, other pharmacotherapies and particularly liraglutide could confer a substantial benefit to those who can afford it, plus we imagine that lifestyle intervention could play an important supplementary role to metformin in those who can tolerate it). No therapies are yet FDA-approved for the treatment of prediabetes - as this population at risk for type 2 continues to grow, we hope to see metformin indicated for diabetes prevention sometime soon, though this would likely require advocacy with patient, physician, and professional groups. In fact, this is going on, but there actually doesn't appear to be much enthusiasm at the FDA from what we hear.

Although popular believe has it that there is little incentive for pharmaceutical companies to push for a prediabetes indication for a generic medication, we don't think that is necessarily true. At any rate, while there certainly is professional enthusiasm, that doesn't appear to be enough to drive regulatory action. Dr. Buse wrapped-up his remarks with a glimpse at future preventative therapies - from insulin-sensitizing agents that slow disease progression to novel treatments that affect islet cell biology - but emphasized that "right now, there's a clear case to be made for using metformin in 2016."

2. Dr. Simon Heller (University of Sheffield, UK) of the International Hypoglycemia Study Group made the case for a revised definition of hypoglycemia. He advocated that hypoglycemia needs to be measured in more depth and proposed a third prong in between <70 mg/dl as an "alert value" and <40 mg/dl as a sign of severe impairment requiring external assistance - <54 mg/dl would be added as an indication of clinically-relevant, severe hypoglycemia, creating a more comprehensive schematic of hypoglycemia in clinical trials and diabetes care. The current classification of hypoglycemia "lacks in important areas," according to Dr. Heller. He pointed out that real-world prevalence of hypoglycemia is five-10x higher than it is in clinical trials, which is especially problematic given that hypoglycemia has a profound effect on a patient's quality of life. The <70 mg/dl marker doesn't necessarily need to be measured in clinical trials, since it's not always relevant to patients and functions more as an alert for people to prevent even lower blood sugar. When glucose falls below 40 mg/dl, patients may already be experiencing severe cognitive impairment, seizure, or coma. Dr. Heller elaborated on evidence for the clinical significance of the <54 mg/dl mark, arguing that this addition would make for a more complete hypoglycemia definition. At this level, children have been shown to have significantly longer reaction time, people's response and ability to recognize hypoglycemia begins to be impaired (exacerbating their risk for future severe hypoglycemia episodes), and arrhythmias are triggered. In the NICE-SUGAR study, investigators found an association between recurring blood glucose <54 mg/dl and increased mortality. In summarizing this data, Dr. Heller highlighted the "clearly important association between glucose of this level and adverse effects." He shared that this suggested change to hypoglycemia classification has been accepted by the ADA/EASD as a position statement, and will be published in *Diabetes Care* and *Diabetologia* simultaneously in January. We're glad to see greater discussion and consensus around the definition of severe hypoglycemia. If adopted by the field, this revision could enhance our ability to quantify hypoglycemia in clinical trials and to treat hypoglycemia in real-world clinics. That said, there may still be some disagreement regarding the exact blood glucose threshold for severe hypoglycemia - while Dr. Alexander Fleming (formerly of the FDA) forecast a convergence toward a single regulatory definition of severe hypoglycemia with a threshold of 54 mg/dl at WCTD 2016, Dr. Phil Cryer proposed a cut point of 50 mg/dl at Keystone 2016. Overall, we'd like to see greater consensus on this point, particularly from a regulatory standpoint so that new therapies can more concretely demonstrate hypoglycemia benefits - we hope that the ADA/EASD position statement will make strides toward this consensus. For more from this fantastic Saturday-morning symposium by the International Hypoglycemia Study Group, see the Detailed Discussion and Commentary section below.

3. In a highly-anticipated WCPD tradition, Dr. Abraham Thomas (New York University Langone, New York, NY) presented a rapid-fire overview of the very latest clinical trial results in the field of diabetes prevention. These trials, all published within the past few months, covered a diverse range of topics, from studies of type 2 diabetes genetic risk to an examination of how city design affects diabetes and obesity rates in its citizens. Below are a few of the most notable from our view:

- **A recent Lancet article determined that PCSK9 genetic variants known for their association with lower LDL cholesterol are also associated with an increased risk of type 2 diabetes,** in addition to higher FPG and increased body weight and waist-to-hip ratio. No association exists between these PCSK9 variants and A1c, fasting insulin, or BMI. Many people with type 2 diabetes use PCSK9 inhibitors to reduce their cholesterol - a potential cause for concern if PCSK9 has diabetes-promoting effects. That said, statins are associated with a known increased risk for development of type 2 diabetes, but the benefits of their cholesterol reduction are widely considered to outweigh the risks. If the cardiovascular outcomes associated with PCSK9 inhibitors match their incredible LDL cholesterol reduction potency, we expect that risk-benefit ratio of the class will look good - that said, their use has been hugely limited to date even with those with FH.

Furthermore, an increased risk demonstrated those with PCSK9 loss-of-function mutations does not necessarily predict an increased risk with PCSK9 inhibitor therapies. We hope the FOURIER CVOT for Amgen's Repatha (evolocumab) will shed some light on the long-term effects of this PCSK9 inhibitor, although we recognize that the trial is not powered for diabetes outcomes. We learned in an earlier talk by Dr. Robert Eckel (University of Colorado, Aurora, CO) that FOURIER's results will likely be presented at ACC in March 2017. We remain hopeful that PCSK9 inhibitor may address some of the residual cardiovascular risk associated with diabetes.

- **An analysis of the EMPA-REG OUTCOME published in *NEJM* , also presented simultaneously at ADA 2016, provided more insight into the renal protective effects of empagliflozin.** Empagliflozin produced a 44% relative risk reduction in doubling of serum creatinine and a 55% relative risk reduction in incident renal replacement therapy. There was no significant difference in the rate of incident albuminuria between the empagliflozin (n=4124) and placebo (n=2061) groups.
- **A *JAMA* study revealed that residents of more walkable neighborhoods had a significantly decreased ten-year incidence of both obesity and type 2 diabetes.** Researchers scored nearly 9,000 Canadian neighborhoods with a validated index of walkability and tracked the citizens' BMIs and diabetes incidence from 2001-2012. People's leisure-time physical activity, diet, and smoking patterns were unrelated to their neighborhood's walkability, but rates of walking and cycling were far higher in more walkable cities. These findings pointing to the importance of the built environment in mediating a certain degree of diabetes and obesity risk, underscoring the importance of efforts like Novo Nordisk's Cities Changing Diabetes to confront the obesogenic environment that characterizes so many urban areas.
- **Another *JAMA* study dissected the interaction between genetic and lifestyle risk factors for coronary artery disease.** Rather expectedly, the combination of unfavorable genes and lifestyle produced the highest risk profile and the combination of favorable genes and lifestyle produced the lowest risk profile. Interestingly the combination of unfavorable genes and favorable lifestyle produced nearly the same risk profile as the combination of favorable genes and unfavorable lifestyle. In fact, lifestyle was so powerful to minimize the effects of genetic risk that among participants at the highest genetic risk, a favorable lifestyle produced a nearly 50% lower relative risk of coronary artery disease.

4. University of Illinois at Chicago's Dr. Ben Gerber presented a skeptical view of mobile health solutions, pointing to the mixed evidence on effectiveness and the lack of empirical evidence on health outcomes (such as CV events). For example, the TEXT ME trial conducted in Australia (n=710) reported that with just four texts/week for six months, patients experienced statistically significant reductions in major risk factors for CV disease including LDL, blood pressure, physical activity, smoking, and BMI. However, similarly-designed studies of text messaging in the US and elsewhere have reported negative results, which leaves a question mark in the literature. Notably, Dr. Gerber mentioned that some pilot studies of text messaging were not as large as TEXT ME, explaining that further research could very well show convincing health benefits, especially when complemented by co-interventions. He maintained an optimistic opinion on the potential for mobile health strategies to enhance diabetes prevention and care, but suggested that we still have a ways to go in identifying optimal evidence-based approaches. Attrition is a common problem in mobile health studies - the recently-published TRIPPA trial found a dramatic decline in Fitbit wear post-intervention, with only 10-15% of participants still wearing the device one year out. Mobile health strategies have to find a way to circumvent attrition and maintain engagement. Dr. Gerber went on to list additional lessons learned from studies of mobile health: Text messages and equivalent alerts should be random rather than predictable to maximize impact on behavior change, and should ideally be relevant to personal context (though this greatly increases the complexity and cost of the approach). For certain desired behavior changes, such as healthier eating, mobile health alerts might incite craving, and should thus be carefully crafted to encourage mindful eating. Dr. Gerber ended his presentation on a positive note, referring to exciting work going on at Omada Health to bring evidence-based elements into new mobile health platforms. He reiterated that these DPP-related platforms could be effective tools for weight management, but

that we should wait for long-term data on health outcomes before touting mobile health as a scientifically-grounded healthcare solution.

5. "A person with diabetes engages with her healthcare team only 0.007% of the time - that's even less for someone with prediabetes." Emphasizing that a majority of diabetes management is *self*-management, immediate past AADE president Dr. Deborah Greenwood presented social media as a powerful tool for the diabetes community. Foremost, Dr. Greenwood (Sutter Health, Sacramento, CA) pointed out that social media is 24/7 - no matter the time of day or night, a patient can ask questions, receive feedback, and connect with others in the Diabetes Online Community (DOC). Since most patients spend a fraction of a percent of time with a healthcare provider, it's important for them to have other reliable sources of psychosocial support, which is absolutely critical in diabetes self-management. This is only one on a list of many benefits to social media - Dr. Greenwood also discussed relationship-building ("diabetes can be lonely"), the sharing of ideas, motivation to cope, shared experiences to combat fear and stigma, culturally-appropriate support regardless of where you are in the world, and spreading health literacy. She acknowledged that social media use is currently more common in the type 1 community vs. the type 2 community and attributed this to greater stigma associated with the latter, though more research is ongoing on this front. As part of the iDOCr (International Diabetes Online Community Research Council), Dr. Greenwood and colleagues are developing research questions with the end goal of optimizing social networking conversations. This program will hopefully address many of the challenges associated with social media for the diabetes community as well - Dr. Greenwood mentioned privacy issues, ensuring the quality and validity of information shared, the current lack of models to evaluate social media platforms, and the digital divide that exists for elderly and minority populations. We look forward to seeing what comes out of the iDOCr, as we agree that more research into optimizing social media would be extremely beneficial for global diabetes care. We so applaud Dr. Greenwood herself for her incredible social media interaction.

- **Dr. Greenwood urged WCPD attendees to engage with social media platforms as well.** She reminded everyone of the official conference hashtag - #WCPD9 - and suggested that if you're new to social media, conferences are a great place to start!

6. Dr. Paolo Pozzilli (University Campus Bio-Medico, Rome, Italy) provided an update on prevention efforts for type 1 diabetes at the primary and secondary levels. For type 1 diabetes, primary prevention entails intervening when two or more type 1-associated islet autoantibodies are present but glycemic control remains normal (stage 1 type 1 diabetes, under the JDRF/ADA staging system). Trials of this kind, which often involve dietary interventions, have had mixed success. For instance, infants with a family history of type 1 diabetes and autoantibody-confirmed risk had decreased incidence of beta cell autoimmunity after several months of drinking formula free of β-casein (Knip *et al.*, 2010) but no such effect was found for infants restricted to a gluten free diet (Beyerlein *et al.*, 2014). Although we are far from having a consensus on viable primary type 1 diabetes prevention efforts, Dr. Pozzilli underscored that large, long-term studies such as the TEDDY trial are underway and may provide important insights on the environmental determinants of type 1 diabetes for children with high genetic risk. Secondary type 1 diabetes prevention entails intervening when an autoimmune response and dysglycemia is detectable but symptoms have not yet appeared (stage 2). Two studies of note have attempted this - the ENDIT trial using nicotinamide and a Finnish study using nasal insulin (Näntö-Salonen *et al.*, 2008) - though neither demonstrated a protective effect versus placebo. Despite the mixed results for type 1 diabetes prevention efforts thus far, TrialNet has a number of ongoing prevention studies enrolling individuals with stage 1, stage 2, and newly-diagnosed type 1 diabetes - we find these very promising.

- **Dr. Pozzilli also discussed the "changing face of type 1 diabetes," forecasting that tertiary type 1 diabetes prevention may soon become an option for preventing complications and disease progression after symptoms have already become manifest.** The main aim of tertiary type 1 diabetes prevention, in Dr. Pozzilli's view, is not to reverse the disease and stop insulin therapy, but to protect the beta cells from complete destruction. He believes this may be feasible with the use of pharmacotherapies originally developed for type 2 diabetes, such as GLP-1 agonists and SGLT-2 inhibitors. The GLP-1 agonist liraglutide (Novo Nordisk's Victoza)

has been demonstrated to reduce insulin requirements in longstanding type 1 diabetes patients (Kielgast *et al.* 2011), and exenatide (AZ's Byetta) administration significantly reduces postprandial blood glucose in people with type 1 diabetes (Sarkar *et al.* 2014) - that said, Novo Nordisk declined to pursue a type 1 diabetes indication for liraglutide following the phase 3 ADJUNCT ONE and TWO trials that revealed concerning safety signals in terms of hyperglycemia with ketosis and hypoglycemia, coupled with modest A1c reduction efficacy. On the SGLT-2 inhibitor front, EASE-1 trial demonstrated the effectiveness of empagliflozin (Lilly/BI's Jardiance) to rapidly reduce insulin dose and improve metabolic control in type 1 patients (Pieber *et al.* 2015).

7. In an engaging debate on the use of SGLT-2 inhibitors in type 1 diabetes, Dr. Kathleen Wyne (Ohio State, Columbus, OH) pointed to the profound weight loss, decrease in blood pressure, and opportunity to educate patients on euglycemic DKA (arguing pro) while Dr. Mick Kumwenda (NHS Trust, North Wales, UK) underscored the DKA risks and lack of sufficient evidence on SGLT-2 inhibitors in type 1 patients (arguing against). Dr. Wyne's position centered around the notion that with proper education - in particular, on managing DKA risk and staying hydrated to avoid genital mycotic infections - a patient with type 1 diabetes can reap major benefits from an SGLT-2 inhibitor, namely A1c reductions, weight loss (which is becoming even more important with the growing prevalence of "double diabetes"), decreased blood pressure, less hypoglycemia, and a lower required dose of insulin. Notably, we've heard this opinion from other leading diabetes thought leaders as well, including Drs. Jeremy Pettus and Anne Peters at ADA 2016. Dr. Kumwenda pointed out, however, that few of these improvements on health markers have been empirically-supported for a type 1 patient population - that is, a large majority of our data on SGLT-2 inhibitors is limited to type 2 diabetes. He cited a study published in *Diabetes Care* showing a significant risk for DKA adverse effects associated with canagliflozin (J&J's Invokana) treatment in participants with type 1 diabetes. Besides, Dr. Kumwenda added, we don't have sufficient high-quality diabetes education as it is, so we can't necessarily rely on this in endorsing SGLT-2 inhibitor use in type 1 diabetes care. To this last point, we only hope that diabetes education continues to improve, as we view it a disservice to patients to restrict prescriptions of potentially helpful drugs based on a distrust in the education component. To date, we're not sure how euglycemic DKA is being reported in studies, so we also look forward to more information on this. Above all, we're excited to see continued conversation on this new class of agents. Dr. Wyne expressed excitement as well over Lexicon's investigations of SGLT-1/SGLT-2 dual inhibitor sotagliflozin in type 1 diabetes, which we agree holds promise based on results from the inTandem clinical development program so far.

8. A lively symposium on nutrition convincingly demonstrated the value of dieting in a macronutrient-selective (rather than macronutrient-eliminating) manner. All of the speakers converged on the notion that opting for unprocessed over processed carbohydrates (that is, whole grain, fruits, and vegetables instead of sugar) and unsaturated over saturated fats (that is, olive oil, nuts, and legumes instead of animal fat and butter) is equally effective - not to mention simpler - than rigorously restricting carbohydrates or fat altogether. Nutritionist Ms. Amy Fisher (Montefiore Medical Center, New York, NY) pointed out that popular diet strategies (low carb, low fat, vegetarian, vegan, paleo, etc.) are actually not as distinct as they appear, sharing a majority of crucial elements in common: limited refined starches, little added sugar, and no processed foods. She surmised her view on the ideal diet with a reference to author Michael Pollan's famed mantra: "eat right, not too much, mostly plants." On a similar note, leading dietician Ms. Anne Wolf (Anne Wolf & Associates, Charlottesville, VA) emphasized the importance of simply eating less, outlining evidence that dietary approaches such as low carb and low fat are essentially equivalent so long as caloric restriction is present. We are reminded of Dr. Donna Ryan's (Pennington Biomedical Institute, Baton Rouge, LA) recommendation that the best diet is simply the one to which someone can best adhere.

- **Perhaps the most surprising information to arise from this symposium came from Dr. Jaakko Tuomilehto's (Dasman Diabetes Institute, Kuwait City, Kuwait) discussion of the Nordic diet.** To parallel the famed Mediterranean diet, the lesser-known Nordic diet (heavy in root vegetables, cabbage, apples, berries, oats, barley, fish, and coffee) is associated with protection against cardiovascular disease and weight gain in RCTs. Dr. Tuomilehto attributes this in part to the

high antioxidant and omega-3 content of these foods native to the northern European regions surrounding the Baltic Sea. Accompanied by an image of his own berry farm in his home country of Finland, Dr. Tuomilehto presented a *JAMA* article of his own to support the protective effects of coffee against type 2 diabetes. To the audible gasps of everyone in the audience, Dr. Tuomilehto revealed that women from Finland (the nation with the highest per capita coffee consumption) who drink >10 cups of coffee per day (!) have a 79% reduced risk of developing type 2 diabetes (HR 0.21; p<0.001; controlled for age, physical activity, BMI, smoking, education, and alcohol consumption). Less prolific coffee-drinkers also benefit from a type 2 diabetes risk reduction: 58% for women who drink 7-9 cups/day, 60% for those who drink 5-6 cups/day, and 27% for those who drink 3-4 cups/day. We're glad to see evidence-based support for our own coffee habits!

9. Dr. Timothy Garvey (University of Alabama, Birmingham, AL) made the powerful argument that effective diabetes prevention must be grounded in meaningful efforts for obesity prevention. One of the original composers of the AACE obesity treatment algorithm, Dr. Garvey overviewed the genetic, biological, and environmental factors that conspire to produce obesity, emphasizing that obesity not a lifestyle choice and its treatment goes far beyond a simple ratio of energy intake and energy expenditure. When obesity is addressed (which is not often the case - as we learned from the ACTION study only 55% of Americans with obesity have received a formal diagnosis, and only 65% perceive obesity as a disease) treatment strategies are typically determined in a BMI-centric framework, whereby an individuals' BMI determines what type of therapy - lifestyle, medications, and/or surgery - is most appropriate. Dr. Garvey argued for a more complications-centric approach, where instead physicians and patients agree upon a personalized treatment strategy together based on the individual's unique obesity complications (sleep apnea, cardiovascular disease, diabetes/prediabetes, etc.) and how they impact their daily life. Lifestyle modification is always the cornerstone of this approach, sometimes in combination with pharmacotherapy or surgery according to careful consideration of efficacy, safety, and cost. Dr. Garvey reflected that, as an epidemic that affects two-thirds of our society, obesity endured a long and difficult road to official status as a recognized disease (the AMA only made this designation as of June 2013, thanks to strong encouragement from AACE and ACC), but is finally beginning to be taken seriously. We hope that a complications-centric approach to obesity management can help patients and the public better understand and address the health risks associated with obesity, while also separating these risks from the aesthetic evaluation of body weight - in this way, we hope that obesity stigma can be reduced (we've heard heartbreaking stories from patients with obesity at the stigmatization they faced from even the healthcare community from providers who were unable to look past their weight to address underlying health concerns). There is certainly cause for optimism, and we hope this change in perception for obesity foreshadows a similar increasing sense of urgency around prediabetes.

10. Ms. Martha Funnell discussed some of the major behavioral challenges relevant to diabetes care and presented strategies to boost patient engagement. Like other diabetes thought leaders, Ms. Funnell (University of Michigan, Ann Arbor, MI) was very negative about the term "noncompliance." "Keep in mind that this is not a problem, it's a symptom of a problem," she stated, suggesting that one key piece of high-quality diabetes care is identifying the problem underlying the low patient engagement. She acknowledged the difficulty that endocrinologists and primary care physicians face when their patients don't seem to be improving, which can make even the most confident healthcare provider feel like a failure. Overcoming this obstacle requires a change in mindset, recognizing that patients do want to lead a healthy life and reorienting one's responsibility as the healthcare provider to find ways to ease the patient's struggle. We're always appreciative of commentary on the immense psychosocial support that's necessary in optimal diabetes care, which is too-often overlooked in discussions of "noncompliance." Ms. Funnell detailed many useful approaches to better communicating with patients, starting with a change in vocabulary to eliminate this antagonizing term (that change can't come soon enough!). Her additional key points for communicating with patients to boost engagement are described below in the detailed discussion and commentary.

11. A workshop on the AACE prediabetes and obesity treatment algorithms discussed the multiple meanings of "prevention." Primary prevention refers to the standard notion of prevention - stopping a disease from occurring. Pursuing this involves interventions that eliminate risk factors: in the

context of type 2 diabetes, this means preventing dysglycemia from ever setting in (likely by promoting healthful food and lifestyle choices). Secondary prevention refers to halting the early progression of a disease with interventions that attenuate the onset of complications and worsening of the disease. This translates to preventing prediabetes from progressing into diabetes (again by promoting lifestyle change, perhaps in addition to metformin). Finally, tertiary prevention refers to minimizing the complications of a disease and minimizing further deterioration. This translates to aggressive diabetes management with a combination of lifestyle modification, oral agents, injectable drugs. Minimizing the societal impact of diabetes clearly requires efforts in all three domains of prevention, but a major theme of the meeting was that early primary prevention measures hold perhaps the greatest potential, especially if promoted at a systemic level. Certainly, primary prevention strategies are often the lowest cost and most widely applicable, but also often receive the least funding and attention in the current healthcare paradigm.

Detailed Discussion and Commentary

Keynote Lectures

PHARMACEUTICAL INTERVENTIONS FOR DIABETES PREVENTION

John Buse, MD (University of North Carolina, Chapel Hill, NC)

Among the many arguments we heard in support of metformin as a prediabetes intervention, Dr. John Buse presented one of the strongest with a compelling economic and evidence-based case for metformin as a population-level prevention strategy. Dr. Buse (University of North Carolina, Chapel Hill, NC) reviewed a number of prevention studies - including the ORIGIN trial investigating insulin glargine (Sanofi's Lantus), the SEQUEL trial investigating phentermine/topiramate extended-release (Vivus' Qsymia), the SCALE program investigating high-dose liraglutide (Novo Nordisk's Saxenda), and the EDIT and Diabetes Prevention Program (DPP) trials investigating metformin - ultimately concluding that metformin should be considered as a first line of defense in people with prediabetes. Dr. Buse underscored that "Saxenda is definitely effective" in stimulating weight loss and delaying type 2 diabetes, but turned to economics to show why metformin is the most reasonable approach to prediabetes. It would cost a little over $4 billion to treat the entire US prediabetes population with metformin vs. >$1.2 trillion to treat this group with liraglutide. Meanwhile, we learned in a separate session that intensive lifestyle intervention as provided by the DPP costs ~$100/person/session - treating 86 million Americans with prediabetes would thus run a bill of ~$1.4 trillion. These numbers make it hard to argue against metformin as a population-level solution for type 2 diabetes prevention (although on an individual basis, other pharmacotherapies and particularly liraglutide could confer a substantial benefit to those who can afford it, plus we imagine that lifestyle intervention could play an important supplementary role to metformin in those who can tolerate it). No therapies are yet FDA-approved for the treatment of prediabetes - as this population at risk for type 2 continues to grow, we hope to see metformin indicated for diabetes prevention sometime soon, though this would likely require advocacy with patient, physician, and professional groups. In fact, this is going on, but there actually doesn't appear to be much enthusiasm at the FDA from what we hear. Although popular believe has it that there is little incentive for pharmaceutical companies to push for a prediabetes indication for a generic medication, we don't think that is necessarily true. At any rate, while there certainly is professional enthusiasm, that doesn't appear to be enough to drive regulatory action.

- **"Right now, there's a clear case to be made for using metformin in 2016."** Dr. Buse wrapped-up his insightful remarks with a suggestion of future preventative therapies - from insulin-sensitizing agents that slow disease progression to novel treatments that affect islet cell biology - but emphasized that metformin is our best option *today* for the great majority of people who could benefit from a preventative pharmacotherapy.
- **Dr. Buse also outlined key characteristics of individuals who will likely benefit most from preventative metformin - namely younger people who are very overweight, with high blood glucose.** In studies of the DPP, metformin was just as effective as intensive lifestyle intervention among participants with BMI >35 kg/m^2 and those in the highest bracket of fasting blood glucose. In contrast, metformin was minimally effective in the oldest participants enrolled and

among those with BMI <30 kg/m². Dr. Buse explained that because metformin is a "very effective glucose-lowering agent," the magnitude of preventative benefit is greatest in people with higher baseline blood sugar. He also mentioned that metformin works particularly well in women with a history of gestational diabetes, now at increased risk for new-onset type 2.

- **Regarding alternative therapies for prediabetes:** Despite a reduced incidence of new-onset type 2 diabetes associated with insulin glargine, Dr. Buse explained that the weight gain and hypoglycemia risk introduced by this therapy outweigh the potential preventative effects. While Qsymia was "quite effective" in SEQUEL, "on the order of 80% risk reduction," he pointed out that the overall incidence of diabetes in the studied population in the trial was moderate to low, which impedes conclusive evidence for a large-scale preventative benefit in the general population. Similarly, the rate of diabetes development in the SCALE study population was ~1% per year, suggesting that, despite liraglutide's potency as a weight loss agent, the preventative benefit has only been demonstrated in a portion of the population that has a low risk of progression to diabetes anyway.

Symposium: Lifestyle and Diabetes

CHANGING THE BEHAVIOR

Martha Funnell, MS, RN, CDE

Ms. Martha Funnell discussed some of the major behavioral challenges relevant to diabetes care and presented strategies to boost patient engagement. Like other diabetes thought leaders, Ms. Funnell (University of Michigan, Ann Arbor, MI) was very negative about the term "noncompliance." "Keep in mind that this is not a problem, it's a symptom of a problem," she stated, suggesting that one key piece of high-quality diabetes care is identifying the problem underlying the low patient engagement. She acknowledged the difficulty that endocrinologists and primary care physicians face when their patients don't seem to be improving, which can make even the most confident healthcare provider feel like a failure. Overcoming this obstacle requires a change in mindset, recognizing that patients do want to lead a healthy life and reorienting one's responsibility as the healthcare provider to find ways to ease the patient's struggle. We're always appreciative of commentary on the immense psychosocial support that's necessary in optimal diabetes care, which is too-often overlooked in discussions of "noncompliance." Ms. Funnell detailed many useful approaches to better communicating with patients, starting with a change in vocabulary to eliminate this antagonizing term (that change can't come soon enough!). Her additional key points for communicating with patients to boost engagement are described below:

- **Providers should adopt patient-centric communication that asks more questions and makes fewer declarative statements.** Ms. Funnell suggested open-ended questions that pave the way for collaborative decision-making, so that patients and providers are coming up with a treatment plan together. Positive questions are just as important as negative ones - ask "what's going well for you?" before "what do you hate the most about your diabetes?".
- **Providers tend to get excited about a path too early. Instead, they should remain solution-neutral to reinforce the patient's participation in collaborative decision-making.** The key message here, according to Ms. Funnell, is that the patient and provider are "in this together." Patients feel more supported and develop a greater sense of self-efficacy when they're given an active role in designing their care plan.
- **Patients care more about how diabetes impacts their everyday life, and less about beta cell biology.** While there's a place for an explanation of beta cells in diabetes education, Ms. Funnell argued that the first priority in communicating with patients should be problem-solving for real-world situations. What are you going to do the next time there's cake at a birthday party, or next Thanksgiving? On a similar note, she articulated the need to avoid medical jargon in talking to patients and their families.

- **Compliance and adherence are not outcomes.** Providers must recognize the complexity of the emotional and behavioral aspects of diabetes that influence decision-making, engagement, and self-management.
- **Providers should communicate that diabetes management is NOT easy, but it IS worth it.** "If we act like it's easy, a patient's struggle feels like a failure, and that's immediately disheartening." As Ms. Funnell put it, we've all started an exercise plan that doesn't quite last, and members of the diabetes care team should use this to empathize with patients and offer psychosocial support.
- **"The patient is an expert on his/her own life; I'm just an expert in diabetes. I value the patient's expertise."** We especially appreciated this sentiment from Dr. Funnell, which underscores the fact that diabetes is just one components of patients' lives and it's important to make

Symposium: Diabetic Hypoglycemia: Questions and Controversies

IMPAIRED AWARENESS OF HYPOGLYCEMIA

Stephanie Amiel, MD (King's College London, UK)

Approximately 40% of people entering the DAFNE (Dose Adjustment for Normal Eating) structured education program in the UK are hypo unaware, according to the great Dr. Stephanie Amiel (King's College London, UK). The DAFNE program is able to restore awareness to some. For others, pumps, glucose sensing technology, and other devices help correct for the unawareness. Still, Dr. Amiel commented that we're left with ~10% of the adult type 1 diabetes population who cannot avoid hypoglycemia or regain their awareness. She discussed three "thinking traps" that perpetuate hypo unawareness for this group: (i) the feeling that low blood sugar won't happen again; (ii) the compulsion to avoid hyperglycemia at any cost (otherwise "I'll ruin my diabetes control"); and (iii) the desire "not to make a fuss" or let lows affect one's life. Dr. Amiel expressed disappointment over these thinking traps, but emphasized that they are not unaddressable - cognitive behavioral therapy could be a particularly powerful tool in addressing these barriers to hypoglycemia avoidance. She reminded the audience that once patients break the habit of repeated lows, or blood glucose <54 mg/dl, their hypo unawareness does dissipate. She also presented pilot data on hypoglycemia awareness restoration training from the DAFNE HART study - unawareness effectively disappeared in 20 patients, and three years later most of these patients remained hypoglycemia-free. A larger, randomized controlled trial of this training method is in the works. Dr. Amiel highlighted the urgent need to confront hypoglycemia in all people with diabetes, even and especially those with stubborn cases of hypo unawareness.

FEAR OF HYPOGLYCEMIA

Linda Gonder-Frederick, MD (University of Virginia, Charlottesville, VA)

Continuing on the theme of the psychology underlying diabetes, Dr. Linda Gonder-Frederick (University of Virginia, Charlottesville, VA) discussed the universal problem of hypoglycemia fear. She shared that the Hypoglycemia Fear Survey, developed at the University of Virginia, has been translated to >60 languages, which goes to show the ubiquity of this problem worldwide. Fear of hypoglycemia stems from numerous factors - Dr. Gonder-Frederick touched upon the impact of hypoglycemia history (even one traumatic episode involving injury can produce significant fear) as well as general anxiety, which predisposes some individuals to hypoglycemia fear more than others. While a small amount of fear can be adaptive - helping people avoid repeat instances of blood glucose <54 mg/dl - she also outlined the adverse effects on quality of life. Hypoglycemia fear has been linked to anxiety, depression, a dampened sense of diabetes self-efficacy, restrictions on normal activities such as travel, and relationship tensions.

PANEL DISCUSSION

Simon Heller, MD (University of Sheffield, UK); Stephanie Amiel, MD (King's College London, UK); Linda Gonder-Frederick, MD (University of Virginia, Charlottesville, VA)

Q: When should we treat hypoglycemia? Should we wait for symptoms, wait till blood sugar <70 mg/dl, or wait till blood sugar <54 mg/dl?

Dr. Heller: If somebody is symptomatic, they should be treated, as long as you confirm that they are in fact hypoglycemic. The alert value of 70 mg/dl is a test, but it really depends on how glucose is trending. Is it going up or going down? Are they about to eat a meal? I don't think you can establish a hard and fast rule. Patients should be educated to recognize their symptoms and take action, but there's no guarantee that the same solution will work every time.

Dr. Amiel: I agree with what's just been said. The identification of <70 mg/dl as an alert to the patient to prevent hypoglycemia is crucial. What we teach our patients with blood glucose monitoring is that they should take action at <70 mg/dl. Patients are more likely to over-treat if they're away from supportive family and friends, so we also teach people what action to take and help them gain confidence. We also teach that treating hypoglycemia at <70 mg/dl is important, otherwise you may stop feeling symptoms and lose awareness. On the flip side, if you can prevent low blood sugars <54 mg/dl, you can regain your awareness.

Dr. Gonder-Frederick: The only thing I'd add is that behavioral context also needs to be considered. If someone is about to drive a car, maybe treat even >70 mg/dl if there's a chance that glucose is trending down. We've unfortunately seen tragic results from parents with type 1 diabetes having hypoglycemia-related accidents when they're caring for small infants.

Q: What additional hypoglycemia education would you provide other than sharing signs and symptoms and explaining the <54 mg/dl marker?

Dr. Amiel: Patients are taught to recognize their personal hypoglycemia symptoms and to think about themselves so they can pick up on extra cues of what works for them. Teaching people the consequences of not treating hypoglycemia is very important, but if people aren't taking swift action, shouting out them louder doesn't work. Think about the psychological barriers to treating hypoglycemia that Linda and I have alluded to this morning. In the HART program, the most common thing people with impaired awareness do is delay - so, perhaps the most important message is "don't wait." Tell patients they have a right to look after themselves and they should exercise that right.

Dr. Gonder-Frederick: Patients aren't taught adequately about the window of opportunity for self-treatment - if they miss that window, they could get themselves into real trouble. Neuroglycopenia is another important topic for family members to understand. I've worked with families where the parents are troubled by behaviors their children exhibit during a hypoglycemic episode, and they simply don't understand that the patient was unable to control behavior during that time.

Dr. Amiel: One thing parents too-often do is over-treat hypoglycemia. It's best to teach avoidance strategies (especially situational ones - after exercise, for instance) and to teach what causes hypoglycemia so that people can more successfully prevent it.

-- by Abigail Dove, Payal Marathe, Helen Gao, and Kelly Close