218th NDDK Advisory Council Meeting
Division of Diabetes and Endocrinology and Metabolic Diseases (DDEMD)
Sub-committee Meeting – Open Session
January 27, 2022

Attendees

DDEMD Sub-committee Members: Dr. David D'Alessio, Dr. Debra Haire-Joshu, Ms. Davida Kruger, Dr. Philipp Scherer, Dr. Elizabeth Seaquist, Dr. Michael Snyder

DDEMD Staff Members: Dr. Kristin Abraham, Ms. Folashade Akanni, Dr. Beena Akolkar, Dr. Guillermo Arreaza-Rubin, Dr. Shavon Artis Dickerson, Dr. Olivier Blondel, Dr. Miranda Broadney, Dr. Henry Burch, Dr. Art Castle, Dr. William Cefalu, Dr. Maureen Monaghan Center, Dr. Brad Cooke, Dr. Thomas Eggerman, Mr. Neal Green, Dr. Carol Haft, Dr. Albert Hwa, Dr. Teresa Jones, Dr. Maren Laughlin, Dr. Jean Lawrence, Dr. Christine Lee, Dr. Ellen Leschek, Dr. Yan Li, Dr. Barbara Linder, Dr. Saul Malozowski, Mr. Louis Martey, Dr. Saira Mehmood, Mrs. Heidi Otradovec, Dr. Sheryl Sato, Dr. Salvatore Sechi, Dr. Corinne Silva, Dr. Lisa Spain, Mr. Kyle Sullivan, Dr. Karen Teff, Dr. Pamela Thornton, Dr. Xujing Wang, Dr. Ashley Xia, Dr. Norann Zaghloul

NIDDK/NIH Staff: Mr. Terry Barnes, Dr. John Connaughton, Mr. Randy Copeland, Dr. Ann Jerkins, Dr. Jaron Lockett, Ms. Van Nguyen, Mr. Will Portobanco, Dr. Griffin Rodgers, Dr. Elena Sandovich, Mr. Lan Tian, Dr. Kenneth Wilkins

Welcome and Approval of September 2021 Sub-committee Minutes (Dr. Cefalu)

Dr. Cefalu welcomed everyone to the DEM Sub-committee Open Session virtual meeting and provided an overview of the agenda. He then introduced and welcomed two new Council members, Dr. Philipp Scherer, and Dr. Haire-Joshu, as well as two Ad-hoc Council members, Dr. Elizabeth Seaquist and Ms. Davida Kruger.

Long-term Outcomes in Youth-Onset T2D: TODAY (Dr. Linder)

Dr. Cefalu introduced Dr. Barbara Linder who presented the long-term of the Treatment Options for Type 2 Diabetes in Adolescents and Youth Study (TODAY). She described the study that was launched in 2002 in response to the emergence of T2D in youth, a phenomenon that increased in the 1990s affecting minority and SES disproportionately, particularly during puberty. Except for metformin and insulin no other drugs were yet approved for diabetes treatment in this age group. The underlying hypothesis was that early initiation of combination therapy in youth-onset T2D would be more effective in promoting sustained glycemic control than standard therapy (metformin alone), and that aggressive treatment of adolescents with onset of diabetes during the period of pubertal insulin resistance would lead to improvement of post-pubertal outcomes.

A multi-center clinical trial was launched where 699 youth with T2D for <2 years, ages 10-17y were randomized to receive metformin, or metformin plus rosiglitazone, or metformin plus a lifestyle intervention (NEJM 366:2247, 2012). The results of the study showed 66% of youth on metformin monotherapy failed to maintain glycemic control, an unexpected result based on the more favorable outcomes reported in adults. Addition of rosiglitazone reduced glycemic failure

by 23%, but this drug was discontinued soon after by the FDA. Although intensive lifestyle was associated with more weight loss at 6 months, this did not translate into sustained glycemic control. These results indicated that this condition in youth is more difficult to manage than in adults. Results were published in the NEJM 366:2247, 2012.

TODAY was followed by TODAY 2 where subjects were followed-up with diabetes care for 3 years, plus an additional 6 years of care in the community with annual visits to ascertain disease progression. The cohort that was followed mimicked the original one and consisted of 500 individuals with T2D. In 2021 (NEJM 385:416) results from this observational study were published. The results indicated poor metabolic control and rapid progression of micro and macrovascular complications. Echocardiographic studies in this cohort showed significant decrease in diastolic and ventricular function with abnormal left ventricular geometry, as well as associations with BMI, BP, A1C, and microalbuminuria. Moreover, pulse wave velocity in these subjects showed increased arterial stiffness indicating a high risk for CVD. These manifested in this cohort with 6 cases of congestive heart failure, 4 MIs, 4 strokes, 3 coronary artery disease, 3 cases of ESRD and 4 amputations. In addition, there were six deaths, three of them linked to CVD, two to multiorgan failure post-surgical sepsis, and one secondary to a drug overdose. Pregnancies outcomes were also ascertained, showing an increase in pregnancy loss, premature birth, preeclampsia, babies born large for gestational age, and an excess of both congenital and cardiac abnormalities. Other findings of these studies indicated more rapid loss of beta function in youth when compared with adults with T2D.

The gaps elicited by these findings highlight the need to better understand the mechanisms underlying the rapid deterioration in beta cell function, to find a better prevention path and effective and safe treatments as well as to better understand this condition, its etiology including puberty, intrauterine imprinting, and early life stressors. To address these issues NIDDK launched an RFA-DK-21-002 Understanding and Targeting the Pathophysiology or Youth-onset T2D. The goal is to form a pediatric consortium to recruit a large cohort of obese, “at risk” youth, follow them through puberty with serial OGTT testing with extensive sample banking and careful health and psychosocial phenotyping. The creation of this cohort may allow for additional analyses and also to perform studies beyond glucose. Applications are due in March 2022. The Q&A section ensued.

Ms. Kruger asked whether these patients were properly transitioned form pediatric endocrinologists to adult endocrinologists, and she pointed out that Medicaid does not provide for the treatment of these young individuals with T2D in contrast what happens with TID subjects. Dr. Linder stated that all participants were connected with an adult provider, but not all participants are actively being seen by a provider for their diabetes. She noted that this data is in the process of being analyzed but does indicate a concerning lack of care for young adults. Dr. D’Alessio indicated that the results from the 2021 paper were really concerning and asked about the efforts to better categorize differences between responders and whether more in depth genotyping may help in answering these questions. Dr. Linder explained different approaches that the study group is pursuing to determine whether there are clinical phenotypes that distinguish responders from non-responders. She also provided a link to a GWAS paper where

most identified SNPs overlapped with genes previously identified in adults (Diabetes 2021;70(4):996–1005). Dr. Snyder suggested capturing the effects of COVID-19 on this complex cohort. Dr. Seaquist underscored the ethical questions that these results trigger given the bad outcomes affecting the minority subjects with poor access to health care.

Cystic Fibrosis Research and Translation Centers: An Update (Dr. Eggerman)

Dr. Thomas Eggerman updated the Council members on the Cystic Fibrosis Research and Translation (CFRT) Centers. He described some of the changes that ensued since their creation in 1982 as the result of a Congressional mandate. He provided some basic information on cystic fibrosis to highlight the importance of the CFRT centers as well as of the research cores and themes at the centers, highlighting the variety of valuable CF research that takes place across this program. Further he added information regarding these projects underscoring some of the themes previously addressed. He concluded stating that significant changes have been made in the requirements for NIDDK mission related CF Center theme, research base, and pilot studies, which include responses to Council suggestions. He added that funding is planned for Cystic Fibrosis Related Diabetes pilots at DK funded Diabetes Centers and Centers for Translation Research in 2022.

In the Q&A session Dr Snyder suggested that NIDDK should encourage collaboration characterizing both the gut as well as the lung microbiota. Dr. Eggerman responded that this is ongoing at the University of North Carolina, Chapel Hill, with Dr. Boucher.

The NIDDK Information Network (dkNET): An Update (Dr. Wang)

Dr. Xujing Wang provided an update on The NIDDK Information Network (dkNET) describing its history and composition She explained that there are many problems and barriers that big data generation is presenting to those that want to explore large databases and data sets. These relate to storage, security, changing technology, lack of common protocols and languages, the evolving knowledge, and the literature, among others. She described the timeline of the funding cycles of this project, 2011-2017, and 2018-2023, and how goals have been and will continue to be met.

From the first funding cycle, Dr. Wang described how the discovery portal was established. She emphasized the creation and implementation of research resource identifiers (RRIDs), now adopted by over 1,700 journals, in improving rigor and reproducibility of biomedical research. Dr. Wang then showed how the second funding cycle expanded the project by adding a component focusing on rigor and reproducibility, a hypothesis center which includes the Signaling Pathways Project (SPP), a data knowledgebase, and an outreach and training component with the launching of summer internships, young investigator pilot funding program, webinars, and educational series supported by dkNET. She added that data form the many NIDDK consortia have been incorporated into dkNET and collaborations continue to expand.

She then described the plan to move forward by continuing to enhance the platform, the need to expand the current stakeholders base, and to develop a more diverse workforce to properly

address unique challenges, needs, and opportunities in diabetes research and care.

In the Q&A session that followed, Dr. Scherer stated that many in the diabetes field are unaware of this resource and asked whether NIDDK should be more proactive in reaching out to communities that may benefit from dkNET. He asked whether RC2 recipients are storing their results in this platform. Dr. Wang indicated that dkNET has not been developed as a data repository, but that there are attempts to link more widely to existing data sets. Several DEM staff underscored that this may be requested in future applications, but to migrate data has been problematic. Dr Snyder suggested to establish collaborations with NHLBI who has programs such as TopMed that has extensive data integration efforts. He underscored the need for researchers to have access to continuous glucose monitoring (CGM) data going forward.

Concluding Remarks (Dr. Cefalu)

Dr. Cefalu thanked the Sub-committee members and DEM staff for their presentations and comments. He noted that DEM looks forward to providing details at a future meeting on the progress made on the programs discussed today. Dr. Cefalu noted that new ideas and suggestions are always welcome. Please send them to him or Dr. Haft.