Sex Differences Across the Lifespan: A Focus on Metabolism
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Sex Differences Across the Lifespan: A Focus on Metabolism

Under the auspices of the Center for Women’s Health Research (CWHR), University of Colorado Denver-Anschutz Medical Campus, a National Conference on Women’s Health Research, entitled “Sex Differences Across the Life Span: A Focus on Metabolism” was organized (September 28-30, 2016) at the Hotel Broadmoor, Colorado Springs, CO. Nearly, one hundred participants, including basic scientists, clinicians, policy makers, advocacy group leaders, federal agency and pharma representatives actively interacted throughout the meeting. Following the welcome address by Judy Regensteiner (Director, CWHR), the opening remarks were made by Pam Shockley-Zalabak, Chancellor, University of Colorado-Colorado Springs and Monica Mallampalli (Vice President, Scientific Affairs, Society of Women’s Health Research, Washington, D.C.). During dinner, John Reilly (Dean, University of Colorado School of Medicine) and Ginger Graham (President & CEO, Two Trees Consulting) spoke about the importance of gender differences in research and lauded the efforts of CWHR for organizing the first annual symposium.

Scientific Session I focused on What are the pregnancy-related determinants of chronic disease later in life?

Yoel Sadovsky (Magee-Womens Research Institute) discussed how placental-specific and maternally imprinted miRNA clusters confer resistance to viral invasion in a process mediated by exosomes. This process could also confer resistance to other tissues and Zika virus invasion. Thus, this is a provocative new hypothesis on how placenta safeguards fetal growth and development.

Laura Brown (University of Colorado School of Medicine) presentation was entitled “Brain versus Brawn: Insights into fetal skeletal muscle growth”. She spoke about sex differences in intrauterine growth restricted (IUGR) infants using the sheep model system. She presented evidence on decreases in amino acid uptake rates, myofiber area and how muscle mass is affected in IUGR.

Lee Nelson (University of Washington Fred Hutchinson Cancer Research Center) discussed a very interesting phenomenon named microchimerism in pregnancy, by which there is a bi-directional transport of, for example, immune regulatory cells (Treg cells) between mother and fetus. Such migratory cells also seem to be transgenerationally transported. While there are mostly benefits of microchimerism to combat autoimmune diseases, there are also instances where detrimental effects manifest. The maternal and fetal microchimerism is very well wide spread and the cells lodge themselves throughout the body. Thus, fetal cells take root in mother and maternal cells take root in child, as a result of microchimerism.

Dana Dabelea (University of Colorado School of Public Health) took a life course approach to pediatric obesity and type 2 diabetes (T2D), from an epidemiological perspective. Originally, she studied T2D in Pima Indians and found an alarming increase of T2D in Pima Indian youth. Her data are extrapolated to other ethnic groups. She presented exciting data on outcomes in siblings when the parental metabolic status was considered before and after obesity. Her data pointed out that 1) intrauterine environment is critical and 2) greater maternal weight gain during pregnancy, regardless of pre-pregnancy BMI, is directly related to fetal obesity and the lifelong consequences in offspring.

Jim Roberts (Magee-Womens Research Institute, Pittsburgh) surveyed the literature on preeclampsia (PE) and the acute and long term consequences for mothers and their infants. PE increases risk for ischemic heart disease in women by > 10 times. There is a clear sex bias- this
disease occurs 65% more in women than men. How infants are affected and what targets are indicative of this disease are still unknown.

**Scientific Session II** focus was *What effects do life transitions have on the risk for obesity?* 

**Wendy Kohrt** (*University of Colorado School of Medicine*) presented on regulation of energy balance by estrogens. She showed data on intact, ovariectomized (OVX) and OVX + E2 rats, *Esr1*−/−, and GnRH agonist treated mice, and in each case, how supplementation with estrogen restores physical activity, decreases in adiposity and increases in muscle mass. Her studies are directly related to changes during female-specific age related transition, menopause, whose hallmark is loss of ovarian function and increased adiposity. Her data nicely showed the benefits of physical exercise on many of the metabolic aspects in menopausal animal models.

**Deborah Clegg** (*Cedars-Sinai Diabetes & Obesity Research Institute*) presented very interesting findings on differences in steroid metabolism in gonad intact or surgically removed male to female and female to male transgender patients. The increased risk for cardiovascular diseases, T2D, insulin resistance, hepatic steatosis – all seemed to be steroid ratio (T/E2) dependent. If manipulated in genetically modified mouse models, her work could result in enormous advances in diagnosing and treating this exclusive class of genetically afflicted patients.

**Dwight Klemm** (*University of Colorado School of Medicine*) in his talk presented evidence that distinct adipocyte populations explain age- and sex-linked differences in body fat distribution. While in men, abdominal fat accumulates with age, in pre-menopausal women, fat is deposited below thigh. Subsequently, abdominal fat accumulates in post-menopausal women. His elegant work with genetically engineered mouse models showed that a drug thiazolidinedione (TZD), stimulates bone marrow derived adipocytes from circulating progenitors differentially in male versus female mice. His adiposity imaging studies have also identified sex differences in the deposition of fat in these mouse models. Identifying markers for these distinct populations and culturing them to study regulatory mechanisms could benefit our understanding of sex differences in adipocyte biology.

**Jed Friedman** (*University of Colorado School of Medicine*) illustrated the challenges in analyzing the maternal microbiome and its impact on the next generation. His work demonstrated that microbiome changes before and after pregnancy. His work further elegantly showed that maternal obesity alters the composition of infant gut and the developing immune system at 2 weeks of life. His work also explained the origins of non-alcoholic fatty liver disease in children.

**Michael Jensen** (*Mayo Clinic*) focused on sex differences in adipose tissue and fatty acid metabolism in human subjects. His elegant work with 3H and 14C labeled heavy isotope fatty acid tracers indicated 1) at any given BMI, women have more adipocytes than men, 2) differences in regional adipose tissue exist, 3) net fat gain is sexually dimorphic, 4) interestingly, sex specific differences exist in upper versus lower body fat distribution between men and women, and finally 5) women recycle free fatty acids better than men.

**Elizabeth Barrett-Connor** (*University of California, San Diego School of Medicine*) made introductory remarks on the following 2 speakers during lunch.

**Nanette Santoro** (*University of Colorado School of Medicine*) presented research agenda for women’s health and sex differences in Ob/Gyn. In her thought provoking lecture, she posed the questions: 1) Why and how do females have a survival advantage over males and what are the
prenatal mechanisms? 2) How does pregnancy constitute a window into the future for both maternal health and the health of offspring? 3) How should we best manage the game-changing capabilities of fertility preservation? And 4) How do hormones and menopause modify a woman’s risk of heart disease? She provided interesting facts and figures. She also questioned why is estrogen good for women below 50 years of age but bad for women older than 50 years of age.

Nanette Wenger (Emory University) summarized a large body of work on cardiovascular disease, which is more prevalent in women than in men and specific aspects of prevention for women. She focused on disparities among women, oral contraceptive and menopause hormone therapy, systemic autoimmune disorders, and hypertension. She suggested smoking cessation, cholesterol management are few effective ways to reduce CVD in women. She also addressed sex differences in use of aspirin for CVD prevention.

Scientific Session III focus topic was What are the sex differences in T2D across the life span? What are the implications?

Jane Reusch (University of Colorado School of Medicine) in her talk re-emphasized the sex differences in T2D across life span and discussed role of life style and implications for CVD outcomes. She presented evidence for diabetes increases CVD risk more in women than men. She also presented benefits of exercise on the outcomes. She further identified eNOS and GLP1 as key molecular players for CVD.

Brian Kennedy (Buck Institute on Aging) started his presentation with an overall theme that aging is a driving force for chronic diseases. His work focused on mTORC1 pathway and systematically identifying upstream and downstream components of this pathway using mutant worms and mice. Very interestingly, these mutants displayed sex specific phenotypes. Since mTORC1 is a target for many drugs currently in use, his work will eventually allow us to judiciously use them in a sex specific manner.

Kristen Nadeau (University of Colorado School of Medicine) focused on sex differences in adolescents with T2D. In her presentation, she showed how T2D in youth is different than T1D and T2D in adults. Another aspect she focused was puberty and how the altered steroid milieu influences various physiological processes differently in men and women. Finally, she identified numerous gaps in knowledge in youth-onset T2D.

Linda Peterson (Washington University School of Medicine) presented how muscle function could get affected by obesity and T2D. She showed tissue Doppler imaging techniques and various biophysical methods including PET tracing using $^{11}$C-labeled palmitate, glucose and lactate precursors. She further presented sex differences in blood flow, oxygen consumption, and myocardial fatty acid metabolism.

Sherita Hill - Golden (John Hopkins University) summarized a vast body of literature on sex differences in CVD risk and outcomes in women and men with diabetes in a life time survey. She pointed that race/ethnic differences guide prevention and therapeutic strategies. Her other notable emphasis was on dwelling into socioeconomic status, health behaviors, poor access to care and quality of care in understanding sex differences in CVD risk factors.

Scientific Session IV focus was on what is the role of exercise and drug therapy in metabolism and diabetes across the lifespan?

Laurie Goodyear (Joslin Diabetes Center, Harvard University) focused on the effects of
maternal and paternal exercise on offspring metabolic health. She systematically presented experimental paradigms using rat models and how exercise (maternal, paternal or both) contributes to offspring health outcomes. Of particular note was her data on maternal exercise before and during pregnancy significantly improves glucose tolerance and decreases in insulin levels in offspring. The best beneficial effects she noticed were when both parents underwent exercise training, there was an additive beneficial effects in offspring. She demonstrated the exercise mediated effects via liver/hepatocytes and these may play a role in metabolic health of offspring. She also considered other factors that include epigenetic, hormonal and placental.

Judy Regensteiner (University of Colorado School of Medicine) presented evidence that men and women with T2D have reduced exercise capacity. She also emphasized the differences in diabetes in women before and after menopause. T2D affects cardiac function, particularly, myocardial perfusion index. Her talk also focused on mitochondrial function and oxygen delivery in T2D. Very interestingly, she presented data on exercise recovery, and pointed if men and women respond differently. She posed the question as to whether women have to exercise more to get the benefits. In people with T2D, functional exercise capacity and response to training are the two most important parameters that one must assess.

Majorie Jenkins (FDA Office on Women’s Health, Texas Tech University Health Sciences Center) presented an elaborate and eye-opening historical account of how federal advocacy policy changed in research and guidance since 1977. She affirmatively addressed that FDA is committed for study of sex differences in drug development. She mentioned that under the current FDA policy, every drug validation must include or justify lack of both sexes in cell and vertebrate animal studies. It is also a policy now to label clinically meaningful differences for preclinical and clinical effects of drugs. Her ultimate message was that women subjects must be incorporated in clinical trials and FDA has established various levels of review of new applications to look into this critical issue.

Scientific Session V focus was on Heart Disease and Sex Differences- the Heart of the Matter Zoltan Arany (University of Pennsylvania) presented very interesting findings on a rare pregnancy (women) specific peripartum cardiomyopathy (PPCM) in a mouse model. Towards the end of his talk, he presented data on extensive genetic variant studies on human patients. The disease occurs only after delivery. It turns out that the preeclampsia marker, soluble Filt1 when injected into non-pregnant females or males causes PPCM. He showed that preeclampsia is strongly associated with PPCM, and together they pose a direct insult to cardiac vasculature. This in turn predisposes to heart disease in women. Their group identified a novel sarcomere protein called TITIN, that is truncated in patients with PPCM. Further genetic studies are in progress in his laboratory.

JoAnn Lindenfeld (Vanderbilt University) provided new insights into heart failure with preserved ejection fraction (EF). EF is the % of blood in the ventricle pumped out with each heartbeat. Normal EF is in the range of 50-55 %. She showed data that cardiac specific drugs work differently in men and women. For example, β-1 adrenergic receptors are downregulated more in women than men as a function of aging. Her extensive clinical studies have shown that total blood volume is the lowest in older women. She also pointed that venous system is very critical for some of the observed differences between men and women.

Noel Bairey Merz (Cedars-Sinai Medical Center) argued that treatments and care for women with CV diseases did not occur until very late when compared to those in men. She mentioned that it took almost 12 years to recognize that women also get heart disease. She
reiterated that women are highly underrepresented in CV clinical trials. She has set up NIH level and multi-institutional committees that defined women inclusion criteria in clinical trials. She emphasized that extensive research is needed to identify risk factors for CVD in women. Such work in the future should impact a variety of disorders in women including gestational disorders and preterm delivery and fetal growth restriction.

*In addition to the above five packed scientific sessions, there was a community breakfast session and 1-hour poster session on Thursday (09-29-16). There were also presentations by three junior faculty members (5’ each) at the end of scientific sessions I-III. There was a networking reception organized on Thursday, 10-29-16, that allowed all the participants to interact and make connections.*

---- T. Rajendra Kumar, PhD