Retributions of a Sedentary Lifestyle: Impact on Insulin Sensitivity and Diabetes — Lessons Learned From Studies on Muscle Mitochondria

Altered fuel metabolism is the main metabolic derangement in diabetes, and mitochondria are the predominant sites of fuel metabolism. K Sreekumaran Nair, M.D., Ph.D., an endocrinology consultant at Mayo Clinic’s campus in Rochester, Minnesota, and his colleagues have been focusing their research on understanding the role of mitochondria in the pathogenesis of diabetes.

Dr. Nair’s studies have shown that insulin deprivation temporarily results in increased energy consumption, but this increased energy is not fully translated within the mitochondria into adenosine triphosphate (ATP), the chemical

**Figure.** In sedentary people, mitochondria — the organelles that convert macronutrients to ATP, the chemical form of energy that can be used for all cellular functions — decline with age. A consequence of declining mitochondrial capacity is the decline in aerobic capacity along with the structural and functional decline of many organs, especially skeletal muscle. These changes lead to insulin resistance and, ultimately, increased cardiovascular-related death. All these changes are partly reversible or preventable by exercising regularly. Abbreviations in the figure: CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.
form of energy that cells use. Dr. Nair explains: “This inefficient fuel utilization by mitochondria during insulin deficiency appears to be the cause of increased formation of reactive oxygen species (ROS), which cause irreversible damage to newly synthesized proteins. Proteins are involved in most body functions, and damaged proteins may explain the decline in many of the biological functions of the body. Obese women who are insulin resistant also have excessive ROS emissions, which potentially can damage proteins and other cellular components.”

It has been shown that muscle mitochondrial biogenesis is enhanced by insulin when supplemented by amino acids and glucose. However, in individuals with type 2 diabetes, unlike in controls without diabetes, increasing insulin from baseline levels to high physiological levels failed to increase muscle ATP production. Moreover, it has been shown that insulin-resistant states, such as polycystic ovarian syndrome (PCOS) in women, lead to altered muscle mitochondrial function. Skeletal muscle mitochondrial couplings and phosphorylation efficiencies are significantly lower in women with PCOS who have insulin resistance than in lean women with insulin sensitivity. Women with PCOS also exhibit high levels of oxidative stress in skeletal muscle, as demonstrated by a higher production of ROS. It has been shown that higher ROS emission reduces insulin sensitivity. After three months of an aerobic exercise training program, women with PCOS displayed enhanced insulin sensitivity concurrent to the improvement of muscle mitochondrial coupling and phosphorylation efficiencies, as well as a reduction in ROS emission.

Dr. Nair’s research has also shown that muscle mitochondrial capacity to produce ATP declines with age in people who are sedentary. Muscle mitochondrial capacity to produce ATP is a major determinant of maximal aerobic or exercise capacity. Dr. Nair notes: “Maximal exercise capacity is a more powerful predictor of mortality than other established risk factors for cardiovascular disease. Studies have shown that mortality in chronic diseases, such as diabetes, hypertension, obesity and hyperlipidemia, substantially increases in people with a lower maximal exercise capacity. Research we performed at Mayo Clinic has found that a decline in the capacity of muscle to produce ATP is associated with a decline in many ATP-dependent processes such as protein turnover, which is critical to maintaining protein mass and quality. As a result, the mass and functional quality of the muscle also declines, further deteriorating the maximal exercise capacity. This decline in muscle mass and strength also causes further lowering of insulin sensitivity and increases the incidence of diabetes, hypertension, hyperlipidemia and cardiovascular-related death.” (Figure)

Dr. Nair continues: “Elderly people who maintain a high-level aerobic exercise program and prevent fat gain have a level of insulin sensitivity that is similar to young people. Moreover, elderly people who maintain a high-level exercise program also prevent age-related declines in
Osteoporosis is widely understood to be associated with low bone mass. Matthew T. Drake, M.D., Ph.D., an endocrinology consultant at Mayo Clinic’s campus in Rochester, Minnesota, says: “It is less well-appreciated, however, that this loss of bone tissue is also associated with significant deterioration of the skeletal microarchitecture. Collectively, these changes in both bone mass and microstructure lead to compromised bone strength and increased fracture risk. Further, while the World Health Organization has defined osteoporosis as bone mineral density (BMD) at the hip or spine less than or equal to 2.5 standard deviations below the young normal mean, more fractures occur in patients with osteopenia than osteoporosis due to the fact that osteopenia is far more prevalent in the population.”

Whereas bone mass declines with aging, so too does bone quality. Dr. Drake explains: “It has been clearly shown that age predicts bone fragility and fracture risk independent of areal BMD determined by dual energy X-ray absorptiometry (DXA) imaging. Thus, for the same areal BMD, a 70-year-old woman has a tenfold or greater risk of fragility fracture when compared with a 30-year-old woman. Importantly, this areal BMD-independent effect of aging has been attributed to decreased bone quality. Potential sources of this age-associated decline in bone quality include trabecular thinning, perforation or loss of connectivity; cortical thinning or increases in porosity; or even changes in bone material properties such as the composition and degree of collagen cross-linking.”

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New Tools to Predict Fracture Risk

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iliac crest (a nonweight-bearing site that is unlikely to fracture) and suffer from an inability to accurately assess longitudinal changes, as biopsy sites are different. Likewise, standard DXA imaging has its own limitations, due to its measurement of bone mineral content over a projected bone area to provide an areal BMD. These stem from the inability of DXA imaging to differentiate cortical from trabecular bone, its provision of a 2-D (areal) measure of a 3-D structure, and its tendency to underestimate BMD of smaller bones and overestimate BMD of larger bones.

Dr. Drake comments: “The recent development of high-resolution peripheral quantitative computerized tomography (HRpQCT) imaging has overcome many of the above limitations. HRpQCT imaging allows for noninvasive bone biopsy at the distal radius and tibia, providing in vivo assessment of bone geometry, true 3-D (volumetric) BMD and microarchitecture at extremely high resolution (60 to 82 μm). Further, HRpQCT imaging allows for the construction of microfinite element models of bone strength that can be used to estimate fracture risk. HRpQCT imaging permits measurement of both trabecular (bone fraction, number, thickness, separation, area and volumetric BMD) and cortical (thickness, volumetric BMD, area, endosteal and periosteal circumference) parameters and exposes subjects to minimal radiation. A recent example demonstrating the utility of HRpQCT imaging involves our work at Mayo Clinic demonstrating the skeletal significance that occurs in patients with monoclonal gammopathy of undetermined significance (MGUS). Although fracture rates are substantially increased in patients with MGUS, whether bone loss occurs in MGUS has remained unclear, with most studies demonstrating no decreases in areal BMD by DXA imaging. To address this directly, we studied 50 subjects with MGUS (mean age of 70 years) by HRpQCT imaging and compared them with 100 control subjects matched for age, sex and body mass index. Whereas areal BMD as assessed by DXA imaging was not different between the groups, HRpQCT imaging demonstrated a highly significant decrease of greater than 10 percent in volumetric BMD as well as significant decreases in trabecular and cortical bone parameters. Together, these changes were associated with significant decreases in bone strength, strongly suggesting that these alterations in bone microstructure are likely important determinants of the increased fracture risk seen in patients with MGUS.”

It is important to note that HRpQCT imaging remains a research investigative tool that has not yet received regulatory approval for clinical use, although at Mayo Clinic there is an active research protocol that allows assessment of bone microarchitecture by HRpQCT imaging in patients with a history of fracture despite normal or near-normal DXA-determined areal BMD (Figure 1).

Whereas access to HRpQCT imaging remains limited, a novel method for assessing bone quality and fracture risk at the lumbar spine has recently been developed. Dr. Drake explains: “Termed trabecular bone score (TBS), this method uses standard DXA spine images to measure texture inhomogeneity — that is, how well-structured or poorly structured the trabecular bone appears when assessed as individual voxels (Figure 2). To do so, TBS utilizes a software program installed on a standard DXA computer to provide an index of bone microarchitecture based upon the assessed trabecular texture. TBS does not require additional scan time or radiation exposure. Importantly, TBS has recently been shown to independently predict fracture risk, to complement standard areal

**Figure 1.** Patients with MGUS have increased cortical porosity and decreased bone strength as measured by HRpQCT imaging.
Quality Health Care in Endocrinology

Making the correct diagnosis and implementing the appropriate treatment to optimize a return to good health for an individual patient is one aspect of quality health care. Ann E. Kearns, M.D., Ph.D., an endocrinology consultant at Mayo Clinic’s campus in Rochester, Minnesota, says: “Today, quality health care includes, but extends beyond, the individual physician and patient, and encompasses a complex team of health care providers committed to redesigning health care into a system without errors, waste, delay and unsustainable costs. Mayo Clinic has a long tradition of this broader view, even though at the time of its development it was not labeled with the terms used today. The integrated multispecialty practice and the organization of its medical records remain key components of the Mayo system even now as the clinic plans a billion dollar transition to a unified electronic medical record system across all its sites. External measures are important drivers of change in how physicians approach quality in the health care they provide. The medical field has defined standards of care for some diseases that are measurable, reportable and comparable across health care sites, which facilitate awareness of deviations and stimulate analysis and change to drive better care. The Mayo Clinic Quality Scorecard tracks care coordination and patient flow, patient survival, health care events with harm, and variation in care.”

Physicians also are held accountable to be part of the change through certification requirements that include engagement in practice assessment and improvement. Although Part 4 of the American Board of Internal Medicine Maintenance of Certification (MOC) program is currently on hold, quality improvement projects continue to be recognized with Part 2 knowledge and self-assessment credit. The Mayo School of Continuous Professional Development was the first institution granted the authority by the American Board of Medical Specialties (ABMS) to award Part 4 MOC and

BMD imaging in patients with low bone mass, and to relate better to fracture risk than does areal BMD in patients with secondary osteoporosis. TBS has recently been integrated into international guidelines from the International Osteoporosis Foundation and the International Society for Clinical Densitometry as a validated risk factor for fracture. Further, the FRAX risk assessment tool has recently added a new feature that allows calculated FRAX scores to be adjusted for TBS. As with DXA imaging, TBS can be used at the time of treatment initiation as well as at subsequent visits, and can even be performed retrospectively on archived spine DXA images to assess previous longitudinal changes in lumbar spine bone quality. Finally, it should be noted that at present TBS can only be used to assess bone quality and fracture risk at the spine, although future studies to better understand its clinical utility at the hip appear likely.”
continuing medical education credit for quality improvement projects, and currently is able to award credit to ABMS diplomates in over 20 of the member specialty boards.

Dr. Kearns adds: “Quality health care is important to all clinicians and patients. Within Endocrinology at Mayo Clinic, practice improvements to drive quality care are the result of physician-led teams. For example, a practice redesign to follow-up care after bariatric surgery led to implementation of group sessions with patients and a dietitian coupled with individual assessment with a physician or nurse practitioner. Patient satisfaction was high and efficiency was improved. Other recent division projects have included improving the time to surgery for patients referred for primary hyperparathyroidism, and improving the rate of evaluation and treatment of vitamin D deficiency from less than 5 percent to greater than 90 percent of patients hospitalized for a hip fracture.

“The Hospital Diabetes Oversight Group is a multidisciplinary group that includes endocrinologists, pharmacists, diabetes nurse practitioners and critical care physicians. This oversight group oversees the hospital practice to meet quality standards and monitors adverse events in the hospital related to diabetes.

“Endocrine trainees at Mayo Clinic are required to participate in a quality improvement project during their training. In the first year of fellowship they receive a daylong boot camp in quality improvement methods. Then they can work as a team or join an ongoing team on a quality-related project. Most endocrine trainees have chosen to pursue their own projects with a staff endocrinologist. On occasion this has led to some interesting findings. For example, one fellow’s group wanted to improve upon hypoglycemia awareness documentation among patients with diabetes. But when the group performed a baseline measure by chart audit, they were surprised to find that about 90 percent of the time documentation about hypoglycemia was performed, so there really wasn’t a large enough gap to pursue a project. Thus, not all of the endocrine fellows’ projects have been successful in terms of resulting in an implemented change to practice, but all have been a great learning opportunity about the process. As fellows graduate and move into other practice environments, the tools of quality improvement will be valuable to their efforts to improve the systems of care within which they work.”

2015 Graduating Endocrine Surgery Fellow

Geoffrey B. Thompson, M.D., program director, poses with graduating fellow Grace S. Lee, M.D. Dr. Lee’s new appointment is in the OhioHealth System Hospitals in Columbus, Ohio.
Left to right, followed by the upcoming appointment:

- Oscar L. Morey Vargas, M.D., Sanford USD Medical Center, Sioux Falls, South Dakota
- Rozalina G. McCoy, M.D., Division of Primary Care Internal Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota
- Raul Ruiz Esponda, M.D., Sanford Diabetes Clinic, Fargo, North Dakota
- Kurt A. Kennel, M.D., program director, Clinical Fellowship in Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota
- Derek O’Keeffe, MB.B.Ch., BAO, Ph.D., National University of Ireland Galway Hospital, Galway, Ireland
- Barbara Gisella Carranza Leon, M.D., Vanderbilt University, Nashville, Tennessee

2015 Graduating Clinical Endocrinology Fellows

The 40th Samuel F. Haines Visiting Professor R. Michael Tuttle, M.D., Memorial Sloan Kettering Cancer Center, with members of Endocrinology and the Thyroid Core Group at Mayo Clinic in Rochester, Minnesota. Seated left to right: William F. Young Jr., M.D., R. Michael Tuttle, M.D., Ian D. Hay, M.D., Ph.D. Standing left to right: Jolanta M. Durski, M.D., Siobhan T. Pittock, M.B., B.Ch., Marius N. Stan, M.D., Vahab Fatourechi, M.D., Stefan K. Grebe, M.D., Ph.D., M. Regina Castro, M.D., John C. Morris III, M.D., Gregory A. Wiseman, M.D., Mabel Ryder, M.D., and Diana S. Dean, M.D.

2015 Samuel F. Haines Visiting Professor
Education Opportunities

15th Annual Mayo Clinic Nutrition and Wellness in Health and Disease 2015
Sept. 25-26, 2015, in Washington, D.C.

Nutrition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. This course — designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff — provides a full-spectrum, in-depth overview of situations and topics that clinicians encounter in the ambulatory setting, including obesity in adults and children, weight management strategies, obesity-associated medical conditions, the role of healthy diets, bariatric surgery and pre- and post-surgery medical management, prevention of common medical conditions through healthy lifestyles, effective ways to provide coaching, nutrition for selected groups, nutrition topics in the news, behavior modification, and resilience, in addition to physical activity and wellness. A culinary demonstration highlights cooking techniques to prepare healthy, great-tasting food. Current clinical topics are highlighted through presentations that offer practical clinical management pearls, interactive case studies and panel discussions. The course will be held at The Mayflower Hotel, Autograph Collection, Washington, D.C.

For more information, visit https://ce.mayo.edu/endocrinology/node/1600 or call 800-323-2688 (toll-free).
Course hashtag: #MayoNutrCME

19th Annual Mayo Clinic Endocrine Update 2016
Feb. 28-March 4, 2016, at Hyatt Regency Maui Resort and Spa in Lahaina, Hawaii

Designed for endocrinologists and interested internists and surgeons, the 19th Annual Mayo Clinic Endocrine Update addresses gaps in medical knowledge and barriers in clinical practice in order to improve the outcomes of patients with endocrine and metabolic disorders. This course spans the full range of endocrinology, through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast roundtable discussions and small-group discussions with experts. Attendees have plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen. The course will be held at Hyatt Regency Maui Resort and Spa, Lahaina, Hawaii. To ensure accommodations at the discounted rate, please make your reservations directly with the hotel by calling 888-421-1442 (toll-free). Identify yourself as a participant of the Mayo Clinic Endocrine Update Course.

For more information, visit https://ce.mayo.edu/endocrinology/node/1600 or call 800-323-2688 (toll-free).