Journal of Diabetes and Its Complications 33 (2019) 13–14

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Long-term effects of insulin resistance on appendicular lean muscle

The U.S. population >65 years is estimated to grow from 46 million in 2014 to 88 million in 2050.[1] Insulin resistance (IR) is an important risk factor for a wide range of adverse cardiometabolic consequences[2] and is also implicated in the process of aging[3] and its major health issues, maintaining lifelong health, in particular cognitive and physical performance.[4] It is increasingly being recognized that exposure to metabolic derangements such as IR in early life or at young ages contributes to adverse health outcomes in later life.[5,6] A growing body of evidence suggests that the pathogenesis of diseases commonly associated with aging such as dementia and sarcopenia unfolds many decades before later-life clinical symptoms manifest. For instance, lower muscle strength indices in children and adolescents have been associated with poorer long-term health outcomes.[7,8] Thus, it is similarly plausible that the intersection of IR exposure and initial changes in muscle structure and function may occur much earlier than previously appreciated. However, it has been unclear when or how early the processes underlying this relationship begin. Indeed, prospective lifespan research that connects early life, childhood and young adulthood exposures with subsequent muscle loss to inform development of appropriate early detection or interventions has been lacking.

Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, Zhong et al., in this issue of the *Journal*, thoughtfully address this gap by providing evidence indicating how IR, as measured in young adulthood, and its trajectories over time may affect appendicular muscle in middle age. These findings are on the basis of data from 7 examinations in 2118 individuals spanning 20 years across early adulthood and midlife. The investigators estimated the trajectories of IR and then classify the participants into distinct, mutually exclusive trajectory groups, which are suitable for capturing the effect of risk exposure and allows for closer scrutiny of the population heterogeneity in the change of IR exposures over the life course. They then examined the relationship of IR trajectories with midlife appendicular lean mass (ALM). In models without adjustment for cardiorespiratory fitness, a high-increasing trajectory of IR over two decades between young adulthood and middle age was associated with lower ALM in midlife among both men and women. In models adjusting for cardiorespiratory fitness, the significant effect remained only among men. These findings extend our prior understanding on the effect of IR on important health outcomes over a significant portion of the life course and indicate that poorer later-life muscle indices may have their roots in early life.

When considered in the context of broader research literature addressing impacts of IR, this paper is highly relevant and has important public health implications. This study sends a clear and important message that longitudinal exposure to IR across early and middle adulthood exerts a lasting effect on skeletal muscle health. Most importantly, the current study design does consider the potential impact of socioeconomic status, which may play a key role in determining health behaviors, nutritional status, and susceptibility to risk factors for chronic diseases of aging. These findings are consistent with the growing body of research documenting that early life exposure to adverse cardiometabolic indices, in particular IR, has a negative impact on a substantial range of health outcomes in later-life. In addition, these musculoskeletal findings suggest the possibility that there may be sensitive or critical periods in early life through young adulthood during which physiological or pathological processes create subsequent biological milieu that favors specific outcomes. In other words, maybe there are critical windows of risk linking IR and muscle loss that point to windows of opportunity for detection and/or intervention. Clinical trials have demonstrated that treating cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia, will benefit future outcomes, events are still common even among individuals with well-controlled blood pressure, glucose, and lipids. This may be due to cumulative exposure over time prior to diagnosis and management of chronically elevated risk factors and conditions that promote these. Substantial target organ injury may have already occurred at the point of clinical diagnosis. Hence, the concept of primordial prevention, which focuses on preventing the development of the risk factors themselves and maintaining risk factors at ideal levels from early life, is critically important to reducing the burden of diseases in later life. Considering the shared pathophysiologic mechanisms between skeletal muscle and cardiovascular health, the findings in this article highlight the increasing importance of primordial prevention in improving long-term, later-life health outcomes.

The mechanisms which account for the reported association between exposure to IR and midlife muscle loss have not been fully elucidated with at least two major theories. First, prevalent cardiovascular disease may drive the relationship between IR and muscle indices. Given the young age of the CARDIA participants, this mechanism is unlikely to explain the finding. An alternative explanation is that IR promotes an initial pathway of injury to muscular health by disrupting the normal milieu perhaps through damage to capillary ultrastructure, inflammation and over time, atrophy. The long-term burden of IR may mediate muscle loss in later life. Although the exact mechanism needs further study, it is clear that the adverse effect of IR on muscle indices may be happening earlier in life than we previously thought and may produce measurable manifestations in later life.

Skeletal muscle is considered an endocrine organ that secretes various myokines which mediate IR.[9] In addition, skeletal muscle is a primary tissue responsible for insulin-mediated glucose disposal and as such has critical impact on an individual's metabolic health and physical function in later life. Therefore, loss of muscle mass contributes to glucose intolerance and promoting gluconeogenesis, which in turn exacerbates IR. Accumulating evidence indicates a close relationship between sarcopenia and IR. It also remains unclear whether differences observed between IR trajectories are consequences of baseline differences in muscle indices (poorer baseline muscle status leads to worse IR trajectories) or whether differences observed between IR trajectories produce differences in follow-up indices of lean muscle. While this

https://doi.org/10.1016/j.jdiacomp.2018.10.019

study is limited by a single evaluation of muscle status at the end of the follow-up period, which precludes inferences about how IR trajectories affect muscular trajectory, as follow-up of the CARDIA cohort continues, the investigators can address some of these issues with subsequent rounds of testing, thereby allowing for a longitudinal analysis of how IR trajectories affect muscle changes over time and their progression. Additional data from longitudinal cohorts that have baseline measurements of muscle status beginning early in life could better elucidate the relationship between IR and muscle indices over the life-course.

The current study provides an important focus on the impact that IR as early as 18 years may have on midlife lean muscle mass. Differences in midlife muscle mass are likely to have long-term ramifications for later life frailty and the development of disability. Since elevations in IR can occur early in life, to truly prevent the accrual of excess risk and to increase the potential for improving indices of lean muscle in midlife, maintaining insulin sensitivity must begin in childhood and adolescence.

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References

1. Federal Interagency Forum on Aging-Related Statistics. *Older Americans 2010: Key Indicators of Well-Being.* Washington, DC: US Government Printing Office. 2010.
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
3. Rowe J, Minaker K, Pallotta J, Flier J. Characterization of the insulin resistance of aging. J Clin Invest 1983;71:1581-7.
4. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res 2007;4:147-52.
5. Poston L, Harthoorn LF, Van Der Beek, Eline M. Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. Pediatr Res 2011;69:175.
6. Morrison JL, Duffield JA, Muhlhausler BS, Gentili S, McMillen IC. Fetal growth restriction, catch-up growth and the early origins of insulin resistance and visceral obesity. Pediatr Nephrol 2010;25:669-77.
7. Ortega FB, Silventoinen K, Tynelius P, Rasmussen F. Muscular strength in male adolescents and premature death: cohort study of one million participants. BMJ 2012;345:e7279.
8. Peterson MD, Gordon PM, Smeding S, Visich P. Grip strength is associated with longitudinal health maintenance and improvement in adolescents. J Pediatr 2018;202:226-30.
9. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol 2012;8:457.