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METABOLISM, AGEING, AND ORTHOPEDICS

WEIGHT AND OBESITY:

Obesity has been shown to be a prominent risk factor for osteoarthritis of the knee. Longitudinal studies have also shown that increases in weight can precede the onset of the osteoarthritic knee. However, in recent years, new evidence has emerged indicating that there is a multifactorial mechanism behind obesity as a risk factor for osteoarthritis, including inflammatory processes along with changes in mechanical loading.

Adipose tissue, rather than being a cell mass of passive storage as previously thought, is an active organ that secretes various agents like adipocytokines such as leptin, resistin, and adiponectin (1). These markers have been found in the synovial fluid and plasma of patients with osteoarthritis. They may influence osteoarthritis through direct degradation of the joint or modification of local inflammatory processes. For example, adipose tissue is found to exacerbate symptoms in the joints of the hands and fingers, even though they are non-weight bearing (3).

Because leptin levels are extremely high in obese patients, it has been proposed that leptin resistance may contribute to joint problems. The leptin receptor has also been found in human chondrocytes, osteophytes, synovium, and infrapatellar fat pad. There has been shown to be a direct correlation between leptin and degree of cartilage degeneration. Adiponectin expression in patients with osteoarthritis was found to be one hundred times higher in the synovial fluid compared to plasma. Its receptor was found in cartilage, bone, and synovial tissues.

Inflammation is a central process in the development of osteoarthritis, and due to their modulating effects on inflammation, adipocytokines may play an important role. Leptin and resistin tend to be associated with inflammation, while adiponectin may be a protective agent by reducing pro-inflammatory cytokines.

Disordered metabolism associated with obesity may play a role in the disease course of osteoarthritis. Altered glucose metabolism and insulin resistance leads to proinflammatory cytokine production. Advanced glycation end products may be associated with collagen stiffness and decreased proteoglycan synthesis, indicating cartilage degradation. In a recent report, middle-aged women who were obese and had at least two cardiometabolic risk factors had more than six times the chance of having knee osteoarthritis compared to other women.

Additionally, obesity dramatically increases the mechanical loading of the joint, which can change the composition and structure of articular cartilage. If the quadriceps muscle is unable to absorb the forces on the knee, then more strain is placed on the cartilage. If muscle strength is lost along with weight gain, then the shock-absorbing ability of the muscles is decreased and can result in an increased load on the cartilage structure. This process of fat gain

and muscle loss has been associated with insulin resistance, which may contribute to the loading of the joint along with initiation of local inflammatory processes.

Sarcopenia, or the loss of skeletal muscle tissue, is a common problem in the elderly but may occur across all ages. The sarcopenic obesity phenotype is characterized by the combination of low skeletal muscle mass and high body fat. The aging process exacerbates this condition, as the elderly tend to undergo concurrent loss of skeletal muscle with increases in adipose tissue. However, even in younger individuals, there are conditions that increase the likelihood of muscle loss, such as diabetes, cirrhosis, and arthritis (2). Poor glycemic control in Type II Diabetes, and even insulin resistance alone, has been shown to lead to sarcopenia as well (3).

The body composition characteristic of sarcopenia has been found in patients with hip and knee osteoarthritis by Karlsson, Purcell, and Visser. However, the loss of muscle strength, also known as dynapenia, rather than simply the loss of muscle mass, appears to be a stronger indicator for adverse outcomes such as metabolic syndrome, insulin resistance, and type II diabetes (13). In addition, dynapenic obesity is associated with more functional limitations and metabolic and cardiovascular risks compared to obesity or dynapenia alone.

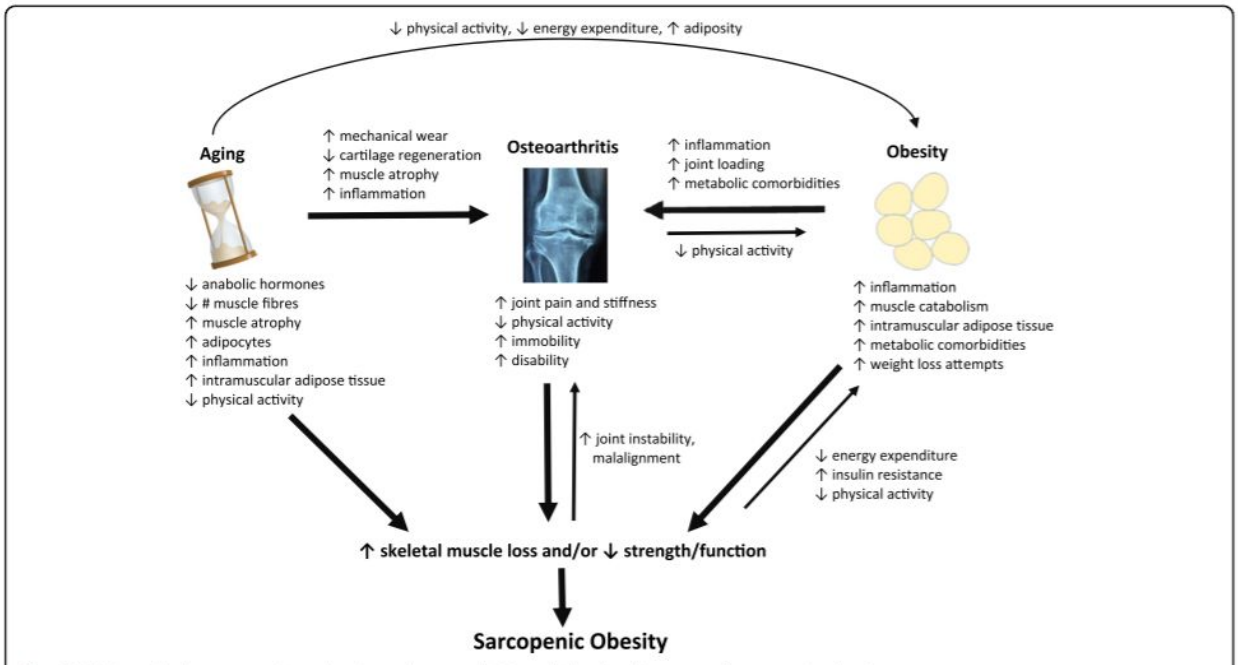

Fig. 1 Relationship between aging, obesity and osteoarthritis and the development of sarcopenic obesity

From Godziuk et al.

PREVENTING AND TREATING DYNAPENIA:

Although loss of muscle mass and strength is common with aging, there are several treatments and methods of prevention which have been shown to be effective for this condition. In general, resistance training is the most effective across all age groups, even in older adults who may be more physically frail. Resistance training programs, usually lasting 8-16 weeks, have been shown to increase muscle strength and muscle mass in older adults, especially when supplemented with whey protein or increased dietary protein intake, or omega-3 fatty acids (13).

One adverse effect of the decreased muscle mass that accompanies aging is a reduction in metabolic rate due to the decrease in metabolically active tissues. This "slower" metabolism can contribute to increased weight gain and adiposity in older adults. However, following a resistance training program is an excellent way to increase an individual's metabolic rate. In fact, one study from the American Journal of Clinical Nutrition showed that 12 weeks of resistance training in older adults (aged 56-80) decreased fat mass, increased fat-free mass (FFM), increased resting metabolic rate, and increased the energy intake needed to maintain weight by 15% (14). Older adults already tend to have a lower metabolic rate than their younger counterparts, but these training programs offer a way to "offset" some of these metabolic losses. Some studies have shown resistance training in older adults to result in better muscle quality as well, so that strength relative to muscle mass increased after the training program (15). Not only does strength increase, but muscle fibers actually become more efficient through resistance exercise.

By implementing a regular weight-lifting program into your routine, it is possible to intake more calories without gaining weight. This is also beneficial for those who are overweight or obese, because the increased metabolic rate allows for more effective fat loss coupled with gains in strength and functional ability. By increasing FFM and decreasing body fat, you decrease your risk for developing insulin resistance, type II diabetes, and high cholesterol. Not only does regular resistance training lower the risk for several metabolic problems, but also has the important benefit of reducing the difficulty of activities of daily living. Many people are concerned that as they age, they will not be able to perform the physical activities that they found enjoyable when they were younger. Weight-lifting programs play an important role in postponing this loss of function in later life, so that you can enjoy independence until a much later age.

DIABETES:

Type II Diabetes is a disease resulting from hyperinsulinemia and insulin resistance. Normally, circulating blood glucose triggers the release of insulin from the pancreas. Insulin then "shuttles" glucose into various tissues, maintaining a relatively constant blood sugar level.

Chronic hyperglycemia (high blood sugar) results from a decreased response of the body's cells to insulin (4). This decreased response is accompanied by a reduction in the ability of the pancreatic Beta cells to produce and secrete insulin. Together, the result is abnormally high levels of circulating blood glucose, which wreaks havoc on several of the body's organ systems. However, higher-than-normal blood sugar levels cause damage regardless of the diagnosis of Diabetes Mellitus. By retrospectively tracking the fasting blood glucose of type II diabetics, a gradual increase in fasting levels can be seen until hitting a "breaking point" when glucose levels increase more dramatically.

Type II Diabetes contributes to abdominal obesity and waist circumference specifically, which are correlated with osteoarthritis (3). Abdominal fat causes inflammatory mediators to be released and reach the joint through the subchondral vasculature. This fat distribution pattern, characterized by excessive abdominal fat, has been linked to OA. Additionally, insulin resistance and Type II Diabetes triggers cartilage degradation through oxidative stress and the accumulation of advanced glycation end products (AGE's).

Type II Diabetes has also been found to be correlated with Osteoporosis, a condition in which bones become weak and brittle generally in the elderly population. This disease affects more than 3 million people each year, resulting in functional limitations. Epidemiological studies have found an increased risk of osteoporotic fractures in diabetic patients (7). The accumulation of AGE's may be one of the causes, as serum levels of AGE's have been found to be higher in those with osteoporosis. In addition, the vascular complications of Type II Diabetes may be a partial cause of bone degeneration.

In a clinical study done by Fatini et al., a group of diabetic patients with peripheral vascular disease had a 32% reduction in circulating endothelial progenitor cells, and the general diabetic group had a 33% reduction in the same cell type (8). As these cells normally play a role in new blood vessel formation and vessel repair, this significant reduction in diabetic patients is detrimental to the blood supply to the bone. Pathological changes associated with diabetes have been known to impair vascular perfusion of bone (9). Prevention of Type II Diabetes may be an important step in preventing subsequent osteoporosis.

Type II Diabetes has also been found to result in diabetic neuropathy, a disorder of the peripheral nerves that can lead to burning, numbness, tingling, and pins and needles sensations especially during the night (18). The pathophysiology of this is not well understood, but the current literature suggests a multitude of reasons that include metabolic factors, oxidative stress, and microvascular impairment that leads to a hypoxic environment for the nervous tissue (19). This can lead to a variety of orthopedic complications from muscular atrophy to most notably foot lesions and possible amputation. Among other effects secondary to diabetic neuropathy are alterations in foot biomechanics and balance issues that can lead to increased fall risks and other

trauma (20). Treatment usually consists of pharmacological intervention with pregabalin, Gabapentin, and antidepressants (21).

PREVENTION AND DIETARY TREATMENT, TYPE II DIABETES:

The low-carb ketogenic diet (LCKD) has been shown to be an effective method of treating patients with Type II Diabetes. Use of the LCKD has had positive clinical outcomes in improving glycemic control, and in one study most patients were able to reduce their doses of diabetes medications or discontinue medications altogether (10). When compared to a low-glycemic diet, the LCKD was more effective in reducing hemoglobin A1C in patients with Type II Diabetes (11). In a study of overweight and obese diabetic patients, the LCKD was more effective than a low-Calorie diet for reducing antidiabetic medication, losing body weight, reducing BMI, reducing waist circumference, and blood glucose levels. It must be noted that because the LCKD is effective in lowering blood glucose levels, patients adhering to this diet must be under close supervision to monitor their doses of diabetes medications.

For certain people, the ketogenic diet may not be a realistic option, depending on culture, lifestyle, or other practical factors. There are additional options for type II diabetics to improve their glucose regulation, metabolic function, and overall health. Time-restricted feeding is a way of eating that involves a limited daily feeding window generally lasting anywhere from 3 to 12 hours, and does not require restricting any particular food group. A review of human and animal studies showed time-restricted feeding to be associated with many health benefits including reductions in body weight, total cholesterol, concentrations of blood glucose, and increased insulin sensitivity (16). Simply by reducing the amount of time you are consuming food throughout the day, you can improve how sensitive your cells are to insulin, improving its ability to reduce blood glucose. When time-restricted feeding was used as an intervention in a mouse model of obesity, pre-existing metabolic disease improved, and there was significant weight loss followed by increased insulin sensitivity and reduced severity of fatty liver disease (17). Time-restricted feeding has several metabolic benefits, as both a preventive and therapeutic method, which may be more practical and easier to implement than a ketogenic diet.

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