Hidden Connections

Professor Yuichiro Eguchi & Dr Hirokazu Takahashi

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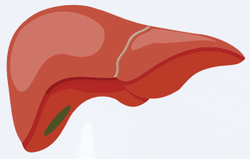
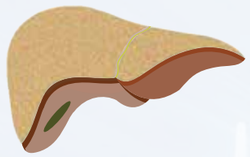
Professor Yuichiro Eguchi teaches for the Division of Hepatology at the Saga Medical School. Dr Hirokazu Takahashi is now a research fellow at the Joslin Diabetes Center in Boston, MA. The two have worked together over a period of years to understand the relationship between liver disease and fat accumulation in skeletal muscle.

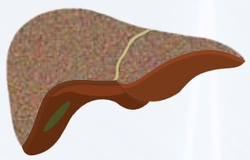
Healthy Liver



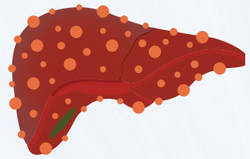
Fatty Liver



Liver Fibrosis



Cirrhois



A Hepatic Manifestation of Metabolic Disease

Non-alcoholic fatty liver disease (NAFLD) has long been associated with visceral fat accumulation, insulin resistance, and type II diabetes mellitus. The work of Eguchi, Takahashi, and their colleague, Dr. Yoichiro Kitajima, began in 2003, when both still worked at Saga University. The researchers grew concerned when the rise in rates of metabolic disease and obesity led to more patients developing NAFLD. It is well-known that aging and obesity cause lipid accumulation in muscle. Skeletal muscle is an important organ in regulating glucose metabolism, and 70% of glucose is absorbed into these tissues. Adipose tissue interbedded in skeletal muscles is thought as “ectopic fat”. Generally, the primary function of adipose tissue in visceral fat and subcutaneous fat is to store lipids, but it also plays an important role in the endocrine system because it secretes enzymes that regulate tissue function across multiple organs. When adipose tissue becomes dysfunctional, the enzymes it excretes lead to the formation of metabolic disorders like type II diabetes and insulin resistance. Adipose tissue’s ability to communicate with many different organs results in something called organ crosstalk.

Organ crosstalk is a concept that is currently being extensively researched, and describes systems within the body that require the involvement of multiple organs. So far, research on visceral and subcutaneous fat has identified crosstalk between fat and multiple organs in NAFLD, but the relationship between the ectopic fat including lipid accumulation in skeletal muscle is not yet well known. The research described here may demonstrate another instance of organ crosstalk and provide insight into how it works. Eguchi, Takahashi and Kitajima consider NAFLD the hepatic manifestation of metabolic disease and have conducted four experiments and published two papers elucidating the relationship between NAFLD and fat accumulation in skeletal muscle. Dr. Kitajima, a Radiological Technician, also developed a novel for measuring lipid accumulation in muscle without which the research presented here would not have been possible. Dr. Kitajima’s methods will allow researchers to finally fully explore the relationship between visceral fat accumulation and NAFLD, and may provide profound insight for the study of organ crosstalk.

Understanding the Language

Fatty liver disease can also be called liver steatosis, and refers to an abnormal retention of lipids in the liver. In addition, 20-30% of NAFLD is thought as non-alcoholic steatohepatosis (NASH) which shows histological inflammation and/or liver fibrosis, and can develop to liver cirrhosis and hepatocellular carcinoma, or liver cancer. The first paper by Eguchi and Takahashi was published in 2009 and primarily uses the term NAFLD, while their second paper was published in 2013 and uses the terms NAFLD and NASH. The two papers refer differently to the skeletal muscle being studied. The researchers specifically chose multifidus muscles, a type of skeletal muscle lining the spine, because its location in the abdomen allowed for the measurement of liver and visceral fat accumulation; therefore, using this tissue also made it possible to estimate the effects of exercise on adipose tissue in skeletal muscle. The 2009 study refers to fat accumulation in multifidus muscles as the ratio of the multifidus muscle attenuation ratio over the subcutaneous fat attenuation ratio (MM/F ratio). Attenuation refers to a reduced level of either the multifidus muscles or subcutaneous fat, and so a higher MM/F ratio indicates that muscle tissue is being lost at a greater rate than subcutaneous fat. In their 2013 study, Eguchi and Takahashi refer to this ratio as intramuscular adipose tissue content, or IMAC. IMAC levels and MM/F ratios, however, refer to the same thing.

The Long and Short of It

Finding a way to demonstrate the relationship between these two different organs required two cross-sectional studies and two longitudinal studies. Cross-sectional studies are designed to be “snapshots” of a population at a certain moment in time, while longitudinal studies collect data over a longer period in order to understand changes over time. In the 2009 paper, 333 NAFLD/NASH patients suspected of suffering from NAFLD/NASH were enrolled in a cross-sectional study. 75 healthy participants were also included as controls. Potential participants whose liver disease could be attributed to alcohol or medications were excluded. The patients’ level of obesity as well as other metabolic indicators such as blood glucose levels were recorded, and MM/F ratios were measured. Measurements of the MM/F ratios were taken using computed tomography (CT), which takes pictures of the inside of the body using x-rays. Eguchi and Takahashi credit the lead author of the papers, Dr Yoichiro Kitajima, with developing the procedure to measure lipid content in skeletal muscle using CT imaging. The results showed that MM/F ratios were much higher in the NAFLD/NASH patients compared to the controls. MM/F ratios also increase with age, height, and are higher in women.

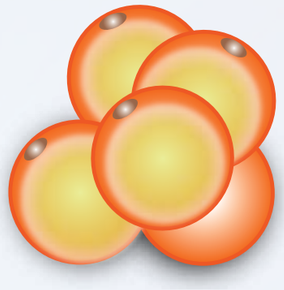
The longitudinal study published in the 2009 paper prescribed a diet and exercise program for patients to examine how visceral fat accumulation and obesity relates to NAFLD/NASH. The patients were then divided into two groups: those that reduced their weight by at least five percent, and those that did not lose weight or lost less than five percent. To evaluate whether weight reduction effected the MM/F ratios, changes in the ratio were compared between the two groups. Over three months, 20 patients achieved the required five percent reduction in weight, while 22 did not. A comparison of the two groups revealed that MM/F ratios were reduced in both men and women who had achieved significant weight loss. Taken together, the cross-sectional study and the longitudinal study together demonstrate that NAFLD/NASH and MM/F ratios are correlated. Lower MM/F levels are also correlated with improved insulin resistance and reduced visceral fat. The results also indicated that MM/F ratios could reflect the severity of fat retention in the liver, and therefore could also indicate whether a treatment for NAFLD/NASH was working or not.

The most important finding is the correlation between liver and skeletal muscle in pathogenesis of NAFLD. It is possible organ cross-talk

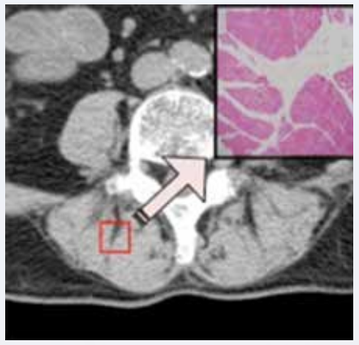
The 2013 paper also presented two analyses, one of which was cross-sectional and one of which was longitudinal. The short-term study enrolled 208 patients. All of these patients had undergone a liver biopsy to diagnose NAFLD/NASH, and again, those that demonstrated excessive alcohol intake or were taking certain medications were not included in the experiment. IMAC levels were again measured using abdominal CT. Bodyweight, height, BMI and insulin resistance were also calculated for each participant, and liver biopsies were also evaluated and used to determine the severity of NAFLD/NASH for each patient. Comparison of all these factors revealed that the severity of NAFLD/NASH is strongly linked with BMI, insulin and IMAC.

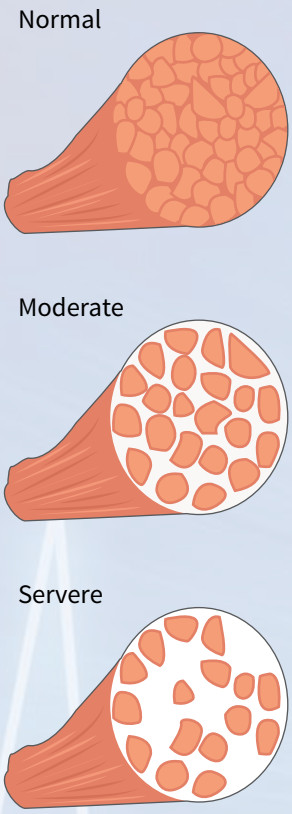
21 patients with NAFLD/NASH were followed for the longitudinal study, and after an average time of 24 months on a prescribed diet and exercise plan, they were divided into two groups. Some patients were also given a combination of drugs designed to treat diabetes and high cholesterol in order to test whether the current treatments for these diseases also result in lower IMAC levels. This time, the groups were divided based on whether their IMAC was reduced. 11 patients improved their IMAC levels; these were the patients who also showed a significant decrease in bodyweight, BMI, and insulin. The results of this second paper strengthen the evidence for a correlation between IMAC levels and pathogenesis of NAFLD/NASH. However, it should be noted that Eguchi , Takahashi and Kitajima do not believe that the research they have conducted so far is extensive enough to conclude that IMAC levels are correlated with NAFLD/NASH severity. In order to prove their hypothesis, they must demonstrate that the measurements they have taken using CT are accurately reflecting fat accumulation in muscle. They are currently working with Boston University to perform both CT and magnetic resonance imaging on mice in order to compare their ability to measure the amount of fat in muscle. Magnetic resonance imaging is considered the gold standard for making these kind of measurements.

Adipose tissue



The results of the longitudinal lifestyle change experiments demonstrated that exercise reduced IMAC levels in NAFLD patients independent of body weight reduction. However, exercise regimens also result in whole-body improvements to glucose tolerance and metabolism, and not just in the reduction of IMAC levels in skeletal muscle. Further in-vivo/in-vitro studies will be able to verify whether improvement of lipid accumulation independently contributes to the amelioration of NAFLD/NASH.





Application of Results in Treatments

Once CT can be demonstrated to be an effective way to measure adipose tissue content in skeletal muscle, it will be an effective marker to indicate severity of NAFLD/NASH and evaluate whether a treatment is effective or not. CT has the benefit of being a low-cost, easy and minimally invasive procedure for both patients and medical providers. In addition to measuring IMAC levels, abdominal CT can be used for visceral fat analysis, to compare spleen fat levels to liver fat levels, and to screen for hepatic tumours and other liver diseases. CT images can also screen for biliary diseases. The biliary ducts are responsible for carrying bile produced by the liver to the bile duct, so it is easy to image this area while also imaging the liver.

In the future, skeletal muscle may one day be the target of treatments for NAFLD/NASH. IMAC was significantly correlated to liver fat, and improvements in IMAC reduced liver fat along with weight reduction. Therefore, it is possible that directly reducing IMAC levels will help ameliorate NAFLD/NASH.

Helping Other Researchers

The work done by Eguchi and Takahashi was very influential in research related to the liver, skeletal muscle and metabolism, and has been cited in many other studies. The results of the experiments published in 2009 were considered in a study by Bertolotti (2014) and his collaborators strategizing how best to treat elderly patients with NAFLD/NASH. Farshad (2013), along with several other authors, used the work on multifidus muscle to examine whether its deformation correlates with nerve root compression, a painful spinal condition. The paper published in 2013 has been cited by metabolic and diabetes researcher Wiernsperger (2013), who used the work done by Eguchi and Takahashi to study how liver sensitivity to insulin levels can contribute to the formation of diabetes. It was also referenced by Del Rocio Ibarra-Reynoso (2014) and her collaborators in their study of hepatic insulin resistance and visceral fat accumulation in school children. The work by these researchers also supported the relationship between fat accumulated in the abdomen and whole-body as well as hepatic insulin resistance.

Both studies were cited by Hamaguchi (2014) and his collaborators. The research conducted by Eguchi and Takahashi helped this group find that patients with high IMAC levels were less likely to survive a liver transplant than those that had lower IMAC levels.

A Long-Term Partnership

Professor Eguchi and Dr Takahashi have been working together for a long time, and now collaborate while separated by both the Pacific Ocean and most of the North American continent. Despite the distance, when asked if they plan to continue working together, they answer “absolutely yes”. In fact, they are currently preparing another article for submission. This new research expands on their previous work and explores the effect of the glucagon-like peptide-1 receptor (GLP-1) on IMAC improvement. GLP-1 agonists, or chemicals that bind to receptors, have already been used as drugs to increase the uptake of insulin and improve glucose regulation. This work strengthens evidence for a possible relationship between insulin resistance and high IMAC levels. Eguchi and Takahashi are also already planning their next research project. The lipid content in skeletal muscle is comprised of both intramyocellular lipids and extramyocellular lipids. They plan to focus on the differences between the two types and would like to clarify the mechanism of correlation between NAFLD/NASH and skeletal muscle in further detail.

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Professor Yuichiro Eguchi was educated at Saga Medical School where he now teaches in the Division of Hepatology. His research focuses on non-alcoholic fatty liver disease, hepatology, gastroenterology and adipose tissue

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