

Prospectus

The Effect of Liposomal KT109 and a Proprietary Drug on Non-Alcoholic
Steatohepatitis
(Technical Topic)

An Analysis of the Stigma Against Overweight People in Healthcare
(STS Topic)

By

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On my honor as a University student, I have neither given nor received
unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-
Related Assignments.

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Introduction

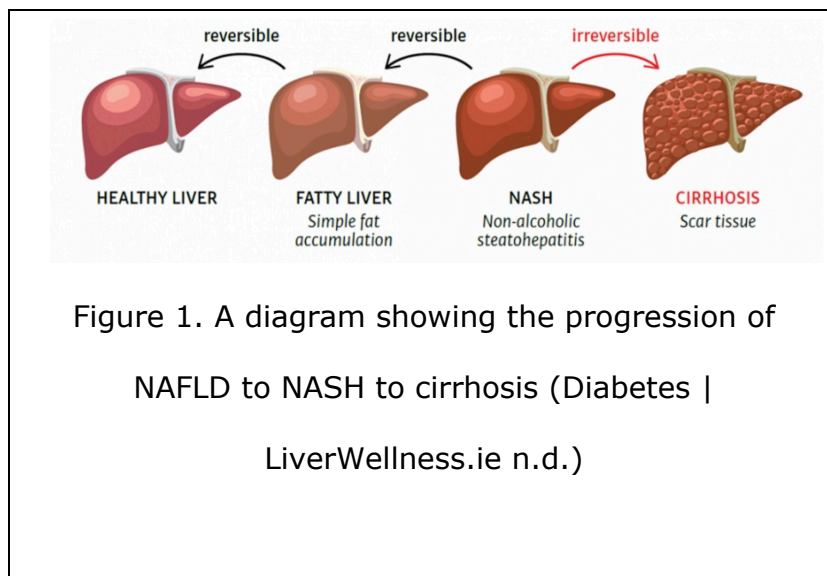
Non-alcoholic steatohepatitis (NASH) is an advanced form of non-alcoholic fatty liver disease (NAFLD), a condition in which there is excess adipose on the liver. With NASH, the buildup of fatty tissue has caused swelling and inflammation within the liver, which if not dealt with, can lead to cirrhosis and liver failure. There are currently almost no medical treatments for NAFLD or NASH, and what does exist typically is for early stage NASH or has toxic side effects. The typical advisement from physicians is for patients to adopt a healthier diet and exercise more in order to lose weight in order to combat symptoms. Augmenting these options, I am studying the effects that a liposome, a nanovesicle composed of lipids, encapsulated with two drugs, KT109 and a proprietary drug, have on reducing liver inflammation. It is our hope that this project will lead to the development of an effective, relatively nontoxic medical treatment for patients with NASH. Of those suffering from NAFLD or NASH, most are people who are classified as overweight or obese. Over the recent years, it has become increasingly evident that the general stigma toward people who are overweight or obese has affected the medical community and leads to a lesser quality of care for these people. The development of certain health markers, such as the body mass index (BMI), have also been used to further stigmatize people of higher weights. As part of my STS capstone project, I am researching both the causes of the stigma and its effects on people who are overweight, both in terms of a lack of care from physicians and the effect it has on promoting obesity and increased weight gain.

Technical Topic

It is estimated that 25% of Americans suffer from Non-Alcoholic Fatty Liver Disease (NAFLD), which is the state of having excess adipose on your liver. NAFLD can be caused by excess eating, especially of high fat and high cholesterol foods, as well as a lack of exercise (Cicero, Colletti, and Bellentani 2018). Figure 1 demonstrates the progression between NAFLD, NASH, and cirrhosis, which is permanent scarring of the liver that could result in need for a transplant. Roughly 20% of NAFLD develop into Non-Alcoholic Steatohepatitis (NASH) (Cicero, Colletti, and Bellentani 2018). Our study proposes a liposomal drug that will reduce the inflammation in the liver, thus reducing the symptoms for patients with NASH. This study is being conducted in the nanoSTAR Institute under the advisement of Dr. Helena Snyder, Dr. Mark Kester, and in collaboration with Dr. Ku-Lung (Ken) Hsu in the Chemistry Department.

Liposomes are nanovesicles that are hollow spheres with an outer lipid bilayer (Woodle and Lasic 1992). These lipid spheres are a beneficial method of drug delivery, especially compared to injection of free drugs because of liposomes' non-toxic properties and

ability to be used for targeted delivery (Kubeček et al. 2015; Sharma and Sharma 1997). The variety of lipids that can be used to form liposomes allow for them to be



heavily altered and tailored for specific drugs. Different methods of preparation can alter the size, charge, and half-life of the liposomes (Gregoriadis and Florence 1993). KT109 is a compound that is an inhibitor of diacylglycerol lipase-beta (DAGL β), an enzyme that regulates inflammation. KT109 has also been found to upregulate AMPK through protein kinase activation, another pathway of reducing inflammation. However, this pathway is not well established. In combination with a proprietary drug, this liposome has the potential to reduce inflammation in the liver without any toxic side effects. The purpose of this project is to analyze the synergistic effects of KT109 and the proprietary drug and establish a clear pathway by which these drugs reduce inflammation. By developing this liposomal drug, we will propose a new medical treatment in order to treat NASH. The establishment of the protein cascade pathway by which these drugs block inflammation will allow us to expand the use of these drugs in order to treat other diseases.

We have previously tested the effects of KT109 in a liposomal form and it was found that 5 microliters of liposomal KT109 can reduce roughly 80% of DAGL β in macrophages in mouse models (Shin et al. 2018). There was also no activity in any other tissue, besides the liver, proving that the liposomal KT109 was nontoxic to the rest of the body. However, we believe that in combination with our proprietary drug, we can further reduce the inflammation in the liver. Overall, this project will develop the long-needed medical treatment for those suffering from NASH.

STS Topic

As previously mentioned, studies have shown that the widespread stigma against people who are overweight or obese has affected the quality of healthcare

received by this group, as well as inadvertently promoted the rise of obesity. As Deborah Lupton describes in her book, titled *Fat*, as a society, we have cultivated the idea that being overweight is not normal and is even a bad thing, reflecting negatively on the person themselves (Lupton 2018). This notion is engrained in our thought processes starting from a young age. In the 1950's, a study done by Richards et al. evaluated children's views towards people of different appearances and abilities (Richardson et al. 1961). In this study, children around the age of ten were asked to rank six images of other children from who they liked best to worst. The images included an overweight child, as well as children with other disabilities such as being in a wheelchair, missing a limb, and having facial deformities; the overweight child consistently ranked last. This research, now almost seventy years old, shows that the stigma against people of heavier weights has existed for decades and has become part of the cultural norm. While it is important that we do our best as a society to reduce negative stigma across the board, this study shows that even within the younger generations, being overweight is seen as being sustainably worse than other "abnormalities". With this preconceived notion being embedded into us at such a young age, it is clear that it would lead to discrepancies within the healthcare field.

The Stigma in Healthcare

In daily life, the stigma people who are overweight face can be frustrating as well as at times overwhelming and dehumanization. However, once this discrimination is brought into the world of healthcare, it can be life-threatening. Disease stigma, an issue that has been around for centuries, is defined by Puhl and Heuer as groups being blamed for the illness and thought to be "immoral, unclean,

or lazy” (Puhl and Heuer 2010). Outside obesity, diseases such as HIV/AIDs in gay men and tuberculosis in African Americans in the 20th century are among other diseases that have had associated stigma with their victims (Puhl and Heuer 2010). Over the decades, healthcare professionals have come to associate specific illnesses with these groups, leaving them at a predisposition to being treated and cared for a specific way. While disease stigma as a whole is an issue that needs to be addressed and dealt with, this paper will focus on the disease stigma and consequential lack of quality care towards people who are overweight and obese.

Recent studies have shown that physicians typically handle their overweight patients with less attention to detail and a lower quality of treatment. In their study, Tomiyama et al. found that although higher-weight individuals are at higher risk for things like ovarian cancer, aggregated data has shown that physicians are less likely to perform pelvic exams on obese individuals (Tomiyama et al. 2018). Similarly, studies show that physicians spend less time with overweight male patients than they do “normal” weight male patients, suggesting they either find them to be less valuable or unable to be helped, unlike “normal” weight patients. It has also been found that the environment of the healthcare provider can negatively affect the health of overweight patients in that, if a patient feels judged, not properly cared for, and unwelcome, this will bar them from seeking medical help in the future (Phelan et al. 2015). Not only does this discouragement for attending a physician put a person at greater risk for a physical illness, it also leads to mental effects, such as depression, higher stress, and anxiety; all of these issues can perpetuate obesity and a person’s struggle with their weight (Phelan et al. 2015).

As more research is done, it is clear that the stigma against people who are overweight or obese is actually perpetuating the issue. By stereotyping and judging this group, we alienate them and cater to the increase in mental illnesses that make it even harder for them to combat their own issues with weight. The outlook that society has created toward overweight people has led the widely accepted myth that being "overweight" is synonymous with being "unhealthy", however, this is not the case. Health is based on a multitude of factors and at times can even be considered subjective. In order to effectively grow towards having a healthier society, both mentally and physically, it is essential that these stigmas are combatted and challenged.

Next Steps

As the above sections suggest, this stigma toward the overweight and obese community puts them at greater risk for both physical and mental diseases. Throughout my thesis, I will analyze both how this stigma affects this group as well as research the "why" behind the stigma. I will focus on the elements of society that have led us to this point, including diet culture, misrepresentation of BMI, and what it actually means to be "healthy". Toward the end of this thesis, I will explore the ways that it can be combatted, both within the medical field and from the source: education, both within young children and medical students. Although misrepresentations in the media are extremely harming and perpetuate the stigma, I believe that in order to truly combat these issues, we must start with the way we educate. I will attempt to gather data to propose ways that education can be

reformed to alter societies perceptions and preconceived notions towards people who are overweight, starting at a young age.

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