**Development of a Novel Liothyronine Delivery System**

(Technical Paper)

**The Role of Stigmatization and Diagnostic Protocols as a Classification System in Diagnosing Autoimmune Hypothyroidism in Women**

(STS Paper)

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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

Hypothyroidism is the term that describes the various etiologies and manifestations of the underproduction or imbalance of thyroid hormones (Patil et al., 2022). An estimated 5% of Americans have been diagnosed with hypothyroidism and another 5% are estimated to remain undiagnosed (Chiovato et al., 2019). However, this is merely one of the numerous estimations that conclude that millions of people are affected by hypothyroidism. Approximately 90% of adults with hypothyroidism are diagnosed specifically with autoimmune thyroiditis or Hashimoto's Disease making it the most common etiology (Amino, 1988). Individuals with this etiology, experience symptoms including but not limited to fatigue, increased sensitivity to cold, constipation, dry skin, weight gain, puffy face, muscle, and joint pain, depression, and impaired memory (McMillan et al., 2008). The current standard of care involves daily oral administration of a synthetic thyroid hormone, levothyroxine (Jonklaas et al., 2014). However, to be treated individuals must first be diagnosed by a physician.

Diagnosis functions as both an event and tool that places a physician “in front of a patient, drawing on a deep and specialized knowledge base in order to identify the cause of a specific case of human discomfort or dysfunction, and to identify a remedy” (Jutel, 2009). Current procedures for the diagnosis of hypothyroidism primarily include biochemical measurements. However, physicians may also consider the individual's symptomology and quality of life measurements (Garber et al., 2012). As stated by the American Thyroid Association (2009), diagnostic procedures for hypothyroidism are not fully standardized allowing physicians to individualize treatment from patient to patient. The standardization within the hypothyroidism diagnostic approach raises many advantages and disadvantages.

Disadvantages of the diagnostic procedures for hypothyroidism include the many symptomatic signals of hypothyroidism that are often stigmatized and overlap with other disease

states. More specifically, symptoms such as weight gain, fatigue, depression, and impaired memory are victims of stigmatization between both general society and physicians (Green et al., 2011; Hunter, 2014; Puhl et al., 2020). Within the medical context, stigmatization can lead to medical gaslighting, resulting in physicians' dismissal or misattribution of symptoms (Moyer, 2022). Stigmatization within the context of symptoms is a result of social influences between both the physician and the patient including gender, social class, race and ethnicity, and household patterns. Within this paper, the effects of these social factors will be discussed and analyzed in relation to the diagnostic classification of patients with Hashimoto's Disease. The advantages of the current diagnostic procedure are argued to be its general success despite its inability to fully treat the patient population (Jonklaas et al., 2014).

Treatment of patients currently dissatisfied with the current standard of care, levothyroxine may require a new technical solution. With the administration of levothyroxine in hypothyroidism patients, problematic symptoms can usually be discontinued and quality of life may be improved. However, thyroxine is not always effective as a treatment method, and symptoms and their repercussions may persist (Jonklaas et al., 2014). Depending on the physician, these persistent symptoms may or may not be addressed due to variable attribution and classification of symptoms, willingness to step outside the standard of care protocols, and physician understanding of the hypothyroidism etiologies. Physicians concerned with the persistent symptoms may consider treatment with liothyronine, a synthetic form of the active thyroid hormone. However, liothyronine can only be administered in very small amounts due to its biochemical properties, limiting its attractiveness as a treatment (Appelhof et al., 2005). Overall improvements could be brought to the field of hypothyroidism by developing a greater

understanding of the role of diagnostic classification systems and the introduction of new treatment therapies to accommodate various etiologies of the condition.

**Technical Topic**

The thyroid is a small butterfly-shaped gland in your neck that produces thyroxine and triiodothyronine hormones. These hormones are responsible for regulating various organ functionalities making their homeostasis critical. Hypothyroidism, a condition in which the thyroid inadequately produces thyroid hormones, presents a thyroidal homeostatic imbalance which is treated with levothyroxine (LT4), a synthetic thyroid hormone. However, sometimes triiodothyronine, the active thyroid hormone, is also administered in small doses to help patients combat persistent symptoms. Ideally, triiodothyronine would be administered in larger dosages but due to limiting chemical and biological properties, it is limited to smaller dosages. Additionally, when prescribing thyroid hormone medications consistent patient compliance is critical. Proper compliance with synthetic thyroid hormones involves medication being taken every day at the same time on an empty stomach. Failure to comply with these protocols can have large implications on the quality of treatment by creating large variations in the patient's levels within an idealized therapeutic range of the drug. Therefore, a continuous liothyronine delivery system should be developed.

Our technical project addresses the inadequacy of currently available oral liothyronine treatment by proposing the development of a novel drug delivery system that will administer a time-sustained release of liothyronine (LT3) over seven days. Approximately 56% of the over 100 million levothyroxine-treated (LT4) patients have been shown to benefit from LT3 therapies (Eligar et al., 2016; Holtorf, 2014). Euthyroid individuals produce thyroxine (T4) and triiodothyronine (T3) to achieve thyroid hormone homeostasis. However, hypothyroid patients

have inadequate production of both of these hormones and are only prescribed synthetic thyroxine or levothyroxine. Many LT4-treated hypothyroid patients still experience symptoms such as chronic fatigue, unintentional weight gain or loss, and poor concentration. Ideally, hypothyroid patients who are not adequately treated by LT4 monotherapies would be effectively treated with the additional administration of liothyronine (LT3). In reality, oral LT3 has a short half-life giving rise to transient peaks and thyrotoxicity. Therefore, a time-sustained LT3 delivery method is necessary to achieve thyroid hormone homeostasis. To address the ineffectiveness of LT4 in this large patient population, we will develop a novel transdermal delivery system that will administer time-sustained release LT3.

The benefits of a transdermal liothyronine delivery system are multifaceted. First, our solution is promising as it alleviates factors associated with patient compliance by limiting administration to once a week. Our system allows this by designing the delivery system with a drug reservoir capable of holding 7 days worth of liothyronine and utilizing a polymer membrane/matrix to limit the diffusion of the drug. Second, our approach negates the negative effects of gastrointestinal bioavailability and absorption issues resulting in improved drug delivery and smaller required dosings. Lastly, by avoiding the gastrointestinal tract, the drug can also bypass the first-pass metabolism further improving absorption and reducing the required amount of drug to reach optimal therapeutic levels. Overall, all of these factors result in more accurate and consistent treatment based on dosing. By providing a more consistent treatment we can hope to normalize the thyroid feedback loop or homeostasis and diminish persistent symptoms in patients that remain dissatisfied with levothyroxine monotherapy.

To reiterate the purpose of the technical project is to develop an alternative drug delivery system for liothyronine to improve treatment outcomes in patients experiencing persistent

symptoms. This technical purpose relates to the sociotechnical purpose as the sociotechnical paper functions to analyze the role that diagnostic protocols play as a classification system in diagnosing hypothyroidism. Furthermore, both of these purposes function to address the inadequate treatment of hypothyroidism patients whether it be due to technical or socio-technical factors.

**STS Topic**

Diagnosis as an event, places a physician "in front of a patient, drawing on a deep and specialized knowledge base in order to identify the cause of a specific case of human discomfort or dysfunction and to identify a remedy" (Jutel & Dew, 2014). As an artifact, diagnosis functions as an integral classification tool in the system of medicine. Outside of being a powerful medical tool, diagnosis serves as an important and powerful social tool. Within the system of medicine, diagnosis acts as a social activity and system with subsequent social consequences.

Primarily, diagnosis confers social status on physicians and can have a large impact on the social status of diagnosed individuals (Jutel, 2014). These events are a social activity wherein physicians utilize labels previously decided upon to enter a patient into a classification system approved by medical taxonomies. This classification system organizes illnesses by identifying treatment options, predicting outcomes, and providing an explanatory framework. The diagnostic classification system gives clinicians the ability to legitimize patient complaints. However, this legitimization also gives rise to social consequences. For example, the legitimization of symptoms permits the patient to act in socially unacceptable ways. Additionally, despite the primary purpose of explaining a patient's condition, diagnosis can also stigmatize and terrify (Jutel, 2009). Sufferers of both mental and physical illness may be marginalized and ostracized because of a diagnosis, shaking the very foundations of one's being (Sadler, 2005).

Within the sociology of diagnosis classification systems, many factors influence the diagnostic outcomes including gender, social class, race and ethnicity, and household patterns (Rose, 2013; Mechanic & McAlpine, 2002). Within the context of hypothyroidism, we can begin to analyze how the majority woman patient population is affected by gender bias in diagnostic classification. More specifically gender bias and stigmatization of symptoms are exemplified in autoimmune hypothyroidism or Hashimoto's Disease, which accounts for approximately 90% of adult hypothyroidism. The majority of Hashimoto patients are women aged between 20 and 60 years old but also generally speaking 75% of patients suffering from autoimmune diseases are women (Amino, 1988; Ramakrishna, 2019). According to a survey from the American Autoimmune Related Diseases Association, 62% of people with an autoimmune disease had been labeled "chronic complainers" by doctors or told they were too concerned with their health (Virginia Ladd, 2019). The compilation of these facts leads us to believe that the large undiagnosed hypothyroidism population results from symptomatic stigmatization in conjunction with the medical gaslighting of women (*Gender Bias in Medical Diagnosis*, 2021).

Many social institutions influence and function within diagnostic classification systems such as disability and social security systems, labor markets, and healthcare organizations that influence the diagnostic classification process (Rose, 2013). Within these social institutions, diagnostic processes serve the administrative purpose of enabling access to services and status, from insurance reimbursement to restricted-access medication, sick leave and support group membership, and so on (Jutel, 2009). It is important to consider and analyze how these factors impact hypothyroidism patients specifically.

**Research Question & Methods**

In addressing the role of diagnostic protocols as a classification system in diagnosing hypothyroidism I will consider the following research question: “How do physicians apply diagnostic classification systems and how does this application impact the diagnosis and subsequent treatment protocols in hypothyroidism patients?” To answer this research question I will utilize discourse analysis, literature review or synthesis, published hypothyroidism patient case studies, and the application of the text “Sorting Things Out” to develop context, a relationship between my technical and socio-technical theses, and an understanding of the power of diagnosis as a classification system and its socio-technical impacts on hypothyroidism patients (Star & Bowker, 1999).

Discourse analysis will be performed within texts on hypothyroidism clinical practice guidelines released by the American Thyroid Association and the American Association of Clinical Endocrinologists to develop context and an understanding of the current diagnostic and treatment recommendations/guidelines provided to physicians. Furthermore, I would like to understand and analyze who is utilizing these documents and how these recommendations from two field-leading associations may inhibit or discourage physicians from individualizing treatment protocols and diagnoses. After developing a comprehensive understanding of hypothyroidism diagnostic and treatment protocols, I will perform a literature review on classification systems to better understand their function and applications and apply this knowledge to my knowledge of hypothyroidism and diagnosis. After developing a deeper understanding of classification systems and the current standards of care and diagnostic protocols of hypothyroidism, I will perform a literature review/synthesis to determine the social role of diagnosis in healthcare. To determine this role I will research further within the field of sociology for analyses of diagnosis, health and illness, disease, and even as specific as hypothyroidism

diagnosis. Lastly, I will utilize case studies of hypothyroidism patients documenting their journeys through diagnosis and treatment to better understand the shortcomings of current diagnostic processes (*Fighting Hypothyroidism Stigma | Everyday Health*, n.d.).

**Conclusion**

Hypothyroidism is an extremely prevalent condition with equal populations of both diagnosed and undiagnosed individuals. To address the effectiveness of diagnosis and treatment both technical and socio-technical initiatives should be taken to improve the ratio between these two patient groups and increase awareness. Once successfully developed, a transdermal liothyronine delivery system would allow further reduction of persistent symptoms in patients dissatisfied with levothyroxine monotherapy creating an outlet for better treatment of hypothyroid patients with differing etiologies and coexisting conditions. Additionally, the transdermal route would facilitate improved patient compliance and outcomes by reducing the number of administrations per week. And lastly, the transdermal delivery system would allow better treatment of subclinical hypothyroidism patients who are not currently treated. Through the sociotechnical thesis, a greater understanding of the hypothyroid diagnostic process and how symptoms are classified and attributed will be gained. From this greater understanding, it will be possible to identify the strengths and weaknesses of said processes and discuss what changes might help improve the patient experience, and the ratio of diagnosed to undiagnosed hypothyroid individuals. Together these theses will function to improve the ratio of diagnosed to undiagnosed hypothyroid individuals as well as improve the ratio of satisfied to dissatisfied hypothyroid patients.

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