Undergraduate Thesis Prospectus

Liothyronine Transdermal Patch: An Optimal Treatment for Hypothyroidism

(a technical research project in Biomedical Engineering)

The Quest for Better Care for Hypothyroidism Patients

(sociotechnical research project)

By

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October 27, 2022

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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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General research problem: The inadequacy of current hypothyroidism treatments

How may treatment of hypothyroidism be improved?

The standard of care for hypothyroidism, levothyroxine (LT4), does not relieve symptoms in one third of patients (Dew et al., 2017). Inadequate thyroid hormone (TH) replacement is associated with increased risk of cardiovascular events, fractures, dyslipidemia, and neurocognitive dysfunction, and with diminished energy, motivation, strength, and quality of life (Dew et al., 2017). The American Thyroid Association (ATA) reported a doubling in the incidence of hypothyroidism in the U.S. in 20 years, from 4 percent in 1996 to 8 percent in 2016 (ATA, 2020). In response, patients, caregivers, medical professionals, advocacies, and researchers have engaged in novel efforts to promote the wellbeing of hypothyroid patients.

Liothyronine Transdermal Patch: An Optimal Treatment for Hypothyroidism

Can medically unmet subsets of levothyroxine treated hypothyroid patients with persistent symptoms be adequately treated with a consistent, slow release, and non-toxic liothyronine monotherapy drug delivery system?

This Biomedical Engineering (BME) Capstone Project is in collaboration with BME student, Haley Barefoot, and department of BME technical advisors, Brian Helmke and Jonathan Rosen.

Euthyroid individuals produce thyroxine (T4) and triiodothyronine (T3) to achieve TH homeostasis. However, hypothyroid patients have inadequate production of both of these hormones and are only prescribed synthetic thyroxine, LT4. Many of these 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 TH homeostasis. Approximately 56% of the over 100 million LT4-treated patients have shown to benefit from LT3 therapies (Eligar et al., 2016; Holtorf, 2014a). In order to address the ineffectiveness of LT4 in this patient population, we will develop a novel delivery system that will administer time-sustained release LT3.

An optimal variation of transdermal delivery methods, to account for LT3's non-ideal molecular weight and short half-life, will be determined by the development of a needs analysis to compile the necessary functions of the system, as well as the identification of design constraints based on a comprehensive literature search of patient populations, marketability, time, cost, materials, and criterial for success. The predicted results are to develop a LT3 transdermal delivery system that meets the needs and constraints in a feasible and effective manner, allowing for but not limited to liposomal based drug vesicles and permeation enhancers.

The selected delivery system design will then be prototyped, tested, and iterated based on success through an *in-vitro* skin model. The developed design must be able to achieve a continuous delivery of LT3. A Successful delivery will be quantified and evaluated based on the mass solute rate through the epidermis to the dermal capillaries, the durability and peel adhesion of the adhesive and backing, and the drug reservoir capacity.

The state-of-the-art LT3 monotherapy extended-release delivery system is a metal-coordinated drug delivery technology, poly-zinc-liothyronine (PZL). While Da Conceicao (2018) found that PZL successfully provides stable circulating T3 levels in hypothyroid rats, PZL is an

oral therapy and is not efficacious for, and therefore marginalizes, patient populations with concomitant gastrointestinal conditions. Various pharmacokinetic factors perturb consistent absorption of the oral formulation from the stomach, and small bowel due to optimal gastrointestinal absorption's dependence on the acidic environment of the stomach. Jonklaas and the ATA (2014) recognize that although short term outcome data in hypothyroid patients have proven to show benefits, longer-term controlled clinical trials of sustained release LT3 must be evaluated before the consideration of the endorsement of synthetic liothyronine therapy for routine clinical use. The inconsistent environment of the bowels with the use of calcium or iron salts and proton pump inhibitors, conditions such as atrophic gastritis and celiac disease, and discordant food and water consumption, impedes the endorsement of synthetic liothyronine use by the ATA. The transdermal delivery of LT3 will bypass the gastrointestinal tract, and its variable absorption, ultimately providing an equitable sustained release LT3 delivery system to be considered for the standard of care treatment of hypothyroidism.

While long-term clinical studies are not realistic in the scope of a capstone project, proof of concept experiments will be conducted to initiate future animal and clinical studies. To prove success of the delivery system, a prototype will be fabricated and a skin mimic will be used to model the circulation mass solute rate of delivery to validate continuous LT3 delivery within the therapeutic range while maintaining a concentration-time derivative close to zero.

A successful project will result in a working LT3 transdermal delivery system prototype capable of time-sustained and constant delivery of LT3, effectually maintaining prolonged T3 plasma concentration levels within the accepted therapeutic range. A non-thyrotoxic and slow-release delivery system is necessary to combat the inadequate hypothyroidism treatment of the

current standard of care. It will steer the patient back towards a physiological TH homeostatic state, regardless of co-morbid gastrointestinal diseases, deiodinase enzyme polymorphisms that limit the conversion of T4 to T3, and the lifestyle influences on therapies currently contributing to over- or under-dosing.

The Quest for Better Care for Hypothyroidism Patients

How are patients, caregivers, associations of medical professionals, advocacies and others striving to promote the wellbeing of hypothyroid patients?

Hypothyroidism is characterized by a deficiency of circulating thyroid hormones, consequently altering both up- and down-stream factors of the thyroid negative feedback loop. These alterations not only affect the biological and physiological aspects of the patient, but they also have a substantial impact on the emotional, relational, and working life of affected individuals. Levothyroxine (LT4) has long been the standard of care for the treatment of hypothyroidism (ATA, 2014). The American Thyroid Association (ATA) has acknowledged that some patients report dissatisfaction LT4 therapy (2014). According to Dew and colleagues (2017), one third of patients with hypothyroidism report no relief of symptoms from it. Yet no alternative non-thyrotoxic drugs have proved more effective than LT4. The proportion of the US population taking synthetic thyroid hormones doubled in 20 years, from 4 percent in 1997 to 8 percent in 2016 (ATA, 2020). Patients, caregivers, medical professionals, advocacies and others have responded to pursuing other means of caring for hypothyroidism patients.

Researchers have served such efforts by demonstrating the deficiencies of LT4 therapy and proposing alternatives. Seeking to improve communication between physicians and patients

and their relatives, Jaeschke and colleagues (1994) evaluated patients' response to LT4 therapy through a health-related quality of life (HRQOL) survey.

Mayor (2018), through a systematic review and meta-analysis, found that thyroid hormone therapy is not correlated to the improvement in symptoms or the general quality of life in patients with subclinical hypothyroidism. The meta-analysis references four studies reported to JAMA, consisting of 858 participants who were allocated either TH therapy or placebo (Feller et al., 2018). It showed no benefits in depressive symptoms, cognitive function, muscle strength, and tiredness. In another study, Mayor (2017), revealed LT4 in not beneficial for elderly patients with subclinical hypothyroidism by assigning 737 participants aged over 65 with subclinical hypothyroidism LT4 or placebo. In the LT4 group, patients reported no significant relief of symptoms, and only a small increase in Thyroid Quality of Life Patient Reported Outcome (ThyPRO). For the treatment of patients who do not respond to LT4 therapy, Thung, Funai, and Grobman (2009) recommend a decision analysis model comparing the cost effectiveness of routine screening of serum TSH levels. The model predicts that universal screening is the dominant strategy with a 589.3 marginal cost per quality-adjusted life year (QUALY) gain for every 100,000 pregnant women screened.

Some medical professionals have called for efforts to improve care for hypothyroidism patients. Such advocacy is consistent with ATA's official mission: "Transforming thyroid care through clinical excellence, scientific delivery and advocacy in a collaborative community" (ATA, 2022). The Substance Abuse and Mental Health Services Administration (SAMHSA) concurs with the advocates: "physical diseases can also present with or mimic mental disorders (e.g. hypothyroidism presenting with or like depression) and need to be identified and treated

accordingly" (SAMHSA, 2020). The American College of Thyroidology (ACT) agrees that "thyroid care needs to improve." ACT's mission "is for people to have the chance to fully recover from thyroid illness" (ACT, 2022).

Some medical professionals favor the development of new hormone replacement drugs and delivery systems and optimization of the current LT4 therapy. Kent Holtorf, M.D. (2014b) emphasizes, "timed-released T3 supplementation should be considered in all depressed and bipolar patients… (and) straight T4 should be considered inappropriate." The Institute of Medical Education (IME) at Jinnah Sindh Medical University and the Jinnah Postgraduate Medical Center's (JPMC) department of internal medicine are advocating to improve the wellbeing of hypothyroid patients by evaluating the environmental trends contributing to adherence and efficacy of LT4 treatments (Kumar & Shaukat, 2019). They attribute low drug adherence to the "need for assistance in taking medication, avoidance of medication with symptomatic relief and busy work schedule." Conversely, they found that regular endocrinologist visits and knowledge about medication contribute to high drug adherence.

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