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A Pilot on the Endocrine Effects of Hormonal Replacement Therapy on Menopausal T1 Diabetics Using Wearable Sensors †

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Abstract: Menopause is an under-reported and under-researched life stage for women living with type 1 diabetes (T1D) despite its lasting approximately 20 years. Menopause is associated with metabolic dysfunction leading to weight gain, impaired insulin sensitivity, hypertension, and hypercholesterolemia, each of which diminishes longevity for women living with diabetes. Its symptoms, affecting cognition, sleep patterns, mood, cardiac and vascular health, and physical health, are known to impact glucose variability dynamics. Associated vasomotor symptoms of hot-flushes/night-sweats, mood swings, anxiety, depression, and sexual dysfunction make it difficult to differentiate between symptoms of menopause and hypoglycemia. While it is recognized that transitioning through menopause increases the potential for developing diabetes, there are no recommendations on managing glucose variability or insulin resistance for women with pre-existing diabetes. Increasingly, women using wearable glucose sensor technologies, insulin pumps, and artificial pancreas systems have self-identified increased glucose variability in the data sets provided by wearable digital health technologies. These datasets, collected in real-time from women outside of traditional research settings, would have been unimaginable 20 years ago. Women highlighting the knowledge deficit are driven to learn and share more about menopause. Their quest for clinician support about the impact of hormone replacement therapies (HRT) on glycemic variability, and the associated risk of developing additional comorbidities, further illustrates the importance of this subject. This work uses datasets from wearable sensors, contributed by women with T1D to inform an understanding of their collective perimenopause and menopause journeys. Glucose readings across a period of weeks, leading up to and immediately following the initiation of prescribed medications, have been analyzed to investigate the physiological effects of HRT on the endocrine system of this sample of menopausal T1D women. Self-management and peer support is bridging the research void, which is why there should be more research into this topic.

Keywords: diabetes; perimenopause; menopause; wearable sensor; insulin pump; hormone replacement therapy; glucose variability; technology; insulin resistance

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1. Introduction

The commencement of menopause signals the end of the female reproductive cycle. It is preceded by menstrual changes to the frequency and duration of menstrual periods, a transitional phase known as perimenopause. With the associated change in levels of the hormones estrogen and progesterone, there is a physiological disruption including, but not limited to, symptoms such as hot flushes, mood swings, loss of libido and loss of bone mineral density [1]. These changes render the needs of menopausal and post-menopausal women as being different from women at different age stages of life [1]. It is estimated that around 10% of the global population comprises menopausal women, with approximately 25 million women experiencing the transition to menopause each year [1].

The nature of menopause makes it challenging to discretely determine; it is not something which occurs at a precise moment [1]. The literature suggests that the definition of menopause is the time following the final menstrual period. If no further menstruation occurs for a period of 12 months, menopause is deemed to have been entered. This is a somewhat ambiguous definition, due to the inability to recognize this immediately, and the specified time span having passed, [1]. This reflects the notion that menopause is a process comprising a steady reduction in the menstrual cycles and finally, the complete end of periods, therein further implying that the process is far from being of a discrete life event [1].

The average age at which menopause occurs has been challenging to pinpoint, but sources suggest that the age in developed and developing countries tends to vary; it has been seen that the average age of women entering menopause in developed countries is around 50 years, in contrast to developing countries, where it may be 40 years [1]. Potential causes of the age disparities between countries include education, diet and income level, all the way towards less recognized factors such as weight, family history and use of pharmacological contraception [1].

To ease the transition into menopause, hormone replacement therapy (HRT) is increasingly used by women as a means of managing those menopausal symptoms resulting from the decline in the normal production of the hormones estrogen and progesterone [2]. Along with regulating a woman's reproductive cycle, estrogen is responsible for maintaining bone density, and vaginal lubrication; thus, an absence of this hormone results in menopausal symptoms such as bone thinning, reduced libido, vaginal dryness and hot flushes [2]. Hence, HRT is an estrogenic surrogate to replace the natural supply of estrogen, which diminishes during the menopausal time [2]. However, it needs to be mentioned that one of the shortcomings of the active assimilation of estrogen is the stimulation of growth in the lining of the womb; thus, progesterone supplementation has to be taken in tandem in order to protect the womb by facilitating the shedding of the uterine lining [2]. Progesterone has neuroprotective and neurochemical benefits, promoting neuroregeneration and enhancing serotonin uptake. The means of administering these exogenous hormones include the use of tablets, gels, vaginal creams and skin patches [3]. The length of time for using HRT varies, but it has been said that prolonged and continuous use of HRT may increase the risk of developing breast cancer [3].

Type 1 diabetes (T1D) represents a chronic endocrine-based disease with onset commencing at any point from birth onwards, although it is commonly diagnosed before the age of 40. It is an autoimmune disease which is characterized by the destruction of pancreatic β-cells. T1D also requires the use of exogenous insulin for survival, where insulin conducts the task of maintaining homeostasis by allowing glucose to enter cells for use as a prime energy source [4]. Epidemiological statistics suggest that 1 in 11 people are living with diabetes, and thus, it has been pinpointed by the World Health Organization (WHO) as one of the four leading non-communicable diseases [4]. HRT treatments have been known to interfere in some capacity with nominal glucose levels, effects of which have not been quantitatively studied extensively yet, but the use of wearable sensors now allows for a means towards tracking this and therein allowing for the inferring of endocrine behavior [4].

Thus, this paper represents a significant study in bridging the impact of hormonal depletion and replacement therapies, namely, menopause and diabetes, by means of research utilizing two months' worth of continuous glucose monitoring data from T1 diabetics, one of whom is on HRT and the other of whom is not, to investigate the effects of prescribed HRT on glucose level variability using data collected from wearable sensors, using the Daily Trend function of NightScout Reporter software.

2. Dataset, Analysis and Discussions

Data were voluntarily provided by two volunteers with type 1 diabetics and utilized the Freestyle Libre2® continuous glucose monitoring system, where participant 1 used

Evorel 50® adhesive patches and Utrogestan 100® oral tablet while participant 2 was not on any form of HRT [5]. Each volunteer provided verbal consent for their data to be used as part of this study. For the analysis, 60 days of continuous glucose monitoring data were utilized, where for the volunteer on HRT, the first 30 days proceeded with the initiation of HRT while the subsequent 30 days followed its initiation as an adjunctive therapy. Thus, for the analysis, the data were broken into two parts, comprising the first 30 days and subsequent 30, in order to be able to investigate and observe glucose level fluctuations and changes that could be occurring as a result of the HRT.

The following statistical metrics were extracted from the glucose readings in order to quantify the series [6]:

- Arithmetic Mean, which can be mathematically expressed as $\frac{1}{N}\sum_{n=1}^{N} x_i$, where N is the total number of samples and x is the nth sample from the segment.
- Standard Deviation (STD) is a metric which provides an indication of how dispersed a sample is relative to the mean and can be mathematically expressed as $\sqrt{\frac{\sum(x_i-\mu)^2}{N}}$, where μ is the sample mean.

The statistical results from the chunking of the data into 30-day blocks can be seen below in Table 1.

Table 1. Results of 30-day block data.

Volunteer	Glucose Level First 30 Days	Glucose Level Second 30 Days	Fluctuations
HRT Volunteer	Mean: 7.29 STD: 2.75	Mean: 7.41 STD: 2.79	Mean: 0.12 STD: 0.04
Non-HRT Volunteer	Mean: 7.53 STD: 2.63	Mean: 7.50 STD: 2.58	Mean: 0.03 STD: 0.05

Interpreting the statistical results from Table 1, it can be seen that the volunteer on HRT had a lower mean glucose level reading. This could be due to the menopausal symptoms manifesting themselves in various ways in the physiology of the HRT volunteer, or due to lifestyle activities, but this cannot be concluded solely from the data presented. In the second half of the data, for the volunteer who commenced HRT, it is evident that their mean glucose level appears to go through an increase, with the dataset identifying the requirement of additional insulin boluses to maintain their time in range. This may be attributed to the presence of the HRT hormones that could be contributing towards the maintaining of the glucose at a higher level, indicating increased insulin resistance similar to that reported during the menstrual cycle. The STD values appear to not fluctuate by any considerable value.

The volunteer who did not access or use HRT appears to have a higher mean glucose level in the first half of the data. There is only a marginal fluctuation in their data within the second half of the data, implying a stable and consistent lifestyle pattern, as well as minimal glucose variability changes over a broad stretch of time. This, when compared with the HRT volunteer, in a sense implies that the use of HRT contributes towards the stabilization and potential increase in the glucose levels of the HRT volunteer. Due to the constrained amount of data, this cannot be firmly concluded from this study, but subsequent work should involve the recruitment of a broader cohort of patients to robustly investigate this theoretical concept further.

3. Conclusions

Menopause represents a closure of the reproductive cycle of a female and is characterized by symptoms which include mood swings and an overall loss of bone mineral density, where its varied nature makes it challenging to explicitly recognize. To help ease the transition towards menopause, HRT is often used by women to help balance for the loss of key hormones such as estrogen, to help ease and steer in the transition towards

menopause. This paper has investigated to a degree the links between menopause with HRT and T1D glucose levels management.

The investigation was carried out using glucose level monitoring data acquired from wearables from two volunteers, both of whom are T1D and going through menopause, but with only one of the volunteers on HRT. The varied nature of the data allowed for the comparison and synthesis for the observation of the effects of HRT on the glucose level of a T1D individual. As part of this, 60 days' worth of data were used for the analysis, split into segments of 30 days, which allowed for the observation of the glucose levels' behavior for the HRT volunteer, who started the HRT treatment around 30 days into the data series.

For the analysis, the arithmetic mean and standard deviation metrics were extracted and used to provide a form of quantification to the glucose level fluctuations across the various defined intervals. The results from the exercise showed an increase in the mean glucose level of the volunteer upon the commencement of HRT, therein insinuating that the HRT treatment contributes, in some fashion, towards the upkeep of the baseline glucose level of a diabetic individual. This notion represents the main observation from the constrained dataset that has been used as part of the analysis. Further work would involve the collection of a broader base of data from a range of patients, to draw a firmer conclusion on the study around the endocrine effects of HRT and its relation towards diabetes glucose level management.

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