Applicant: Dr. Fabiano A. Gomes MD, MSc, PhD

Project Proposal - ***Clinical Efficacy and Metabolic Safety of Ketogenic Diet in Midlife Women with Major Depressive Disorder.***

Background - Major Depressive Disorder (MDD) is a prevalent and quite disabling condition that affects 1 in every 5 Canadians (300 million people worldwide), Women are more vulnerable than men (2-to-3 fold) (Otte et al, 2016), particularly during certain 'windows of vulnerability'(Soares and Zitek, 2008). Despite recent advances in the management of depression, achieving symptomatic remission and functional recovery remains a challenge for at least one third of patients. (Lam et al., 2016). Systemic and metabolic factors have been associated with emotional and behavioral manifestations of depression, suggesting that this condition could in fact constitute a systemic illness (McIntyre at al, 2007). The menopausal transition has been identified as one of the windows of vulnerability for depression (new or recurrent) across the female life span (Soares, 2019). The menopausal transition is also a time of risk for weight gain, lipids abnormalities, diabetes and metabolic syndrome (Stachowiak et al, 2015). Women treated with antidepressants or receiving estrogen-based therapies may experience symptomatic relief; the presence of residual depressive symptoms, however, could lead to frequent relapses, recurrences and poorer quality of life (Soares, 2019). Effective, safe, affordable and acceptable options that target life-style and metabolic changes could represent a novel therapeutic approach to depression. Hence, the safety and efficacy of specific nutritional interventions for depression in midlife women, such as ketogenic diet, should be considered and carefully investigated.

The ketogenic diet (KD) is a high-fat, adequate-protein, low-carbohydrate diet that forces the body to use ketones from fat tissue rather than carbohydrates as the main energetic source (Caraballo & Vining, 2012). Robust clinical data supporting the benefits of KD for the treatment of epilepsy (Bostock et al., 2017). The putative efficacy of KD for depression has been primarily evaluated in animal models (Murphy et al., 2004); a few case reports of individuals with treatment resistant MDD and bipolar disorder also revealed improvements with KD (Bostock et al., 2017). Several health-related outcomes commonly seen with KD could also be potentially beneficial for midlife women with depression, including the beneficial effects on body mass index (BMI), insulin resistance, metabolic syndrome and possibly vasomotor symptoms (Castellana et al., 2019). The KD seems to be well tolerated and its main side effects tend to be transient - most commonly gastrointestinal complaints that last at most for a few weeks.

We herein propose KD as a metabolic treatment for the treatment of Major Depressive Disorders (MDD)(Brietzke et al. 2018). We aim to investigate the efficacy of KD to mitigate the severity of depressive symptoms in midlife women MDD and evaluate the metabolic safety of this intervention.

Study design - Single arm Open-label Clinical Trial

Studied Population, inclusion/exclusion criteria: Twenty women aged 45-55 years in menopause transition or early postmenopausal staging (STRAW + 10 criteria) experiencing depression of at least moderate severity (MADRS scores ≥ 20) will be enrolled into a 12-week study. Diagnosis of MDD will be confirmed by the Mini International Neuropsychiatric Interview (MINI). Subjects will be recruited through the Departments of Psychiatry (Mood Disorders Clinic) and Obstetrics and Gynecology at

Queen's University. Exclusion criteria will include 1) major medical comorbidities (e.g. diabetes mellitus, kidney stones, hyperlipidemia, morbid obesity, heart and liver conditions), 2) acute medical illnesses, such as viral/bacterial infections; 3) specific eating/dietary habits affecting the efficacy of or adherence to KD (e.g., vegan, vegetarian, religious fasting, lactosis intolerance); 4) previous adverse events with ketogenic/low carb diets; 5) vitamins deficiencies, malabsorption conditions; 6) other major psychiatric diagnoses; 7) presence of suicidal ideation; 8) inability to prepare meals following recipes. Eligible Inidividuals could be medication-free or receiving antidepressants on a stable dosing for at least 6 weeks prior to study entry ; if the latter, the dosing of antidepressants should remain unchanged for the duration of the 12-week intervention with KD.

***Intervention*:** At the study entry, a dietician will instruct participants on how to prepare meals (3 meals per day) with 20 g to 30 g of carbohydrates (green vegetables and salad), and 80 g to 100 g of protein (meat, fish, fowl, eggs, shellfish and cheese). Polyunsaturated and monounsaturated fats will also be included in the diet. In-person orientation (1.5-hour session) plus written information on KD along with recipes and suggestions for different meals and menus will be provided. Caregivers or other family members directly involved in planning and preparing meals will also be informed. Customized suggestions will be based on food preferences, eating habits, seasonal availability of food and costs to increase study adherence. Supplemental vitamins and minerals will also be given. Food diaries will register daily intake of solid and fluids throughout the study. The adherence to the KD intervention and proper achievement of ketonic state will be checked weekly through food diary and capillary blood ketone assessment. A one week run-in phase will precede the study. Only those testing positive for ketones in urine will be enrolled.

Outcomes: The primary outcome measure will be the improvement in depressive symptoms based on changes in Montgomery-Asberg Depression Rating Scale (MADRS) total scores; secondary outcome measures will include changes in anhedonia (SHAPS and DARS scores), quality of life (MENQoL) and menopause-related symptoms (Greene Climacteric Scale scores and sub-scores) from baseline to endpoint. Ketones in urine will be weekly assessed. Clinical assessments will occur at baseline and at 2, 4, 8 and 12 weeks; metabolic profile (serum fasting glucose and serum lipids), bone density biomarkers (CTX-1 and PINP - procollagen type I N propeptide) and sexual steroids will be evaluated at baseline and at 12 weeks. Approval by the institutional review board and written informed consent will be obtained prior to enrollment. Treatment will be discontinued in case of 1) unacceptable weight loss; 2) serious treatment-emergent symptoms; 3) severe worsening of depression; 4) protocol non-adherence. This pilot study has the potential to open new avenues for research on dietary interventions for the treatment of midlife women with depression.

Applicant: Maria P. Velez, MD, PhD

Risk of Primary Ovarian Insufficiency in Adolescent and Young Adults with non-gynecological cancer in Ontario: A population-based cohort study

Background:
Primary Ovarian Insufficiency (POI), or menopause before age 40, can result in long-term health effects such as infertility, osteoporosis, cardiovascular disease, impaired mental health, and sexual dysfunction.[1] Female survivors of Adolescent and Young Adult (AYA, aged 15-39 years) are at risk of POI. Depending on patient factors, cancer diagnosis, and treatment exposures, the prevalence of POI in survivors of AYA cancer ranges from 2.1% to 82.2%[2] compared to 1% in the general population.[3] Given that these studies were performed in cohorts treated >20 years ago (before risk-adapted protocols and new potentially less gonadotoxic agents were introduced), it is difficult to predict how the prevalence of POI will compare in survivors of AYA cancer today.
What is the epidemiology of cancer in female AYAs in Canada? The incidence of cancer in female AYAs rises steadily from 2.9% in 15-29 years-old almost doubling to 5.5% in 30–39 year-olds.[4,5] The personal, societal and socioeconomic impact of AYA cancer is high given the approximately 50-60 year life expectancy of survivors.[6] The most common non-gynecological cancer, accounting for more than 80% of new female AYA cancer cases in Canada are thyroid, breast, melanoma, colorectal, Hodgkin lymphoma, non-Hodgkin lymphoma, and brain.[5] All, except melanoma have been studied in relation to POI,[2,7,8] but the risk of women treated with more recent treatments has not been quantified at the population level.
What are the risk factors for POI of female AYAs with non-gynecological cancer? Cancer treatments that cause follicular atresia and destruction of the follicular pool can lead to POI. Alkylating agents and pelvic irradiation pose the greatest threat to ovarian function. The magnitude of risk depends on multiple patient and treatment factors. At patient level, age, sex, type and stage of cancer, and genetic factors are important determinants, with age being the leading factor in women. In regards to treatment, total cumulative dose of alkylating agents, radiation to sensitive organs (e.g. pelvis, brain), and surgery to fertility organs (e.g. Oophorectomy in carriers of BRCA 1/2 mutations) will contribute independently to POI. [9]

Objective: To determine the risk of POI in female AYA cancer survivors of non-gynecological cancer in Ontario

Methods: Design: Retrospective matched population-based cohort study using the Ontario cancer registry (OCR) linked to health administrative data sets

Patient selection: Female AYAs aged 15-39 years at cancer diagnosis will be identified using the OCR. All patients registered in the OCR between January 1st 1992 (when datasets became reliably linkable) and December 31 2011 (to enable substantive follow-up) will be included in the cohort. We will exclude women who died within five years of diagnosis (to enable at least five years of follow-up), or were registered in OCR for a previous malignancy, or were not continuously eligible for provincial health insurance coverage for at least seven years after diagnosis (or until death). In order to compare the risk of POI of women exposed to cancer, a female control population of unexposed women (cancer-free women) will be selected using the Registered Persons Database (RPDB). Eligible women from the general population will be matched to the female AYAs with cancer at a ratio of five unexposed women per 1 exposed woman based on calendar year of birth and census subdivision using a similar approach to Baxter et al. [10] Controls will be assigned a referent date that corresponded to the date of diagnosis in the matched survivor. Controls will be excluded if they had a diagnosis of cancer

prior to the referent date (determined through linkage with the OCR), died within five years of the referent date, or were not continuously eligible for provincial health insurance for at least seven years after the referent date. We will identify women who had undergone a procedure consistent with surgical sterilization (tubal ligation, bilateral oophorectomy, hysterectomy) based on OHIP and CIHI-DAD codes. Survivors and controls with evidence of surgical sterilization at any time prior to diagnosis or up to 12 months after diagnosis or referent date will be excluded.

Exposure: We will include female AYA diagnosed with thyroid cancer, breast cancer, melanoma, colorectal cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, and brain cancer since these account for 80% of female non-gynecological AYA cancer in Canada.

Outcome: POI will be defined as physician visit claims coded as ICD 9-627 in women younger than 40 years.[11] Women with diagnosis of menopause previous to cancer diagnosis will be excluded from the analysis. To increase the accuracy of POI, we will conduct a sensitivity analysis using data from the Ontario Laboratory Information System (OLIS), available at ICES since 2007.[12] Women with at least 2 FSH (Follicle-Stimulating hormone) values in the menopausal range (on the basis of the maximum threshold of the laboratory assay used) will be diagnosed with POI if <40 years.[13]

Data Analysis: Exposed and Unexposed women will be followed in the cohort using administrative databases until December 31, 2016. For each group, we will calculate descriptive statistics for study variables. Log-binomial regression models will be used to calculate the risk of POI or early menopause after cancer by cancer type adjusted by sociodemographic characteristics. **Covariates multivariate analysis:** Patient factors such as age, parity at the time of cancer, socioeconomic estimates (e.g., Income quintiles, deprivation index, and census subdivision, rurality) and immigration status will be considered in adjusted models. **Power calculations:** Thus far, we have identified 14,024 survivors and 59,694 unexposed (cancer-free women) AYAs 15-39 years from 1992 to 2011 (Table below shows the distribution). This will result in a power higher than 80% to detect differences of at least 10% between exposed and unexposed women.

	Cancer survivors	**Unexposed**
Brain	**574 (4.0%)**	**2,517 (4.1%)**
Breast	**3,782 (26.4%)**	**15,755 (25.8%)**
Colorectal	**361 (2.5%)**	**1,510 (2.5%)**
Hodgkin	**1,240 (8.7%)**	**5,516 (9.0%)**
Melanoma	**2,181 (15.2%)**	**9,342 (15.3%)**
NHL	**742 (5.2%)**	**3,208 (5.3%)**
Thyroid	**5,144 (35.9%)**	**21,846 (35.8%)**
TOTAL	**14,024**	**59,694**