The Association Between Diabetes (Type 1, Type 2 and Gestational Diabetes) and Age at Natural Menopause: Results from the Canadian Longitudinal Study on Aging (CLSA)

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Abstract

Over the past few years, the prevalence of diabetes has steadily increased across the globe. With growing incidence of youth onset diabetes more women are expected to spend a larger proportion of their reproductive years with diabetes. It is important to understand the long-term implications of premenopausal diabetes on women's reproductive health including their age at natural menopause (ANM). The present thesis aims to use a large cohort of females to investigate the association between pre-menopausal type 1 diabetes, type 2 diabetes and gestational diabetes, and ANM. Baseline data from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging was used for this analysis. Females who reported having premenopausal diagnosis of diabetes were considered exposed. Kaplan-Meier cumulative survivorship estimates and multivariable Cox regression models were used to assess the association between different types of diabetes and ANM. Various socio-demographic, lifestyle, and premenopausal clinical factors were adjusted in the final model as covariates.

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List of abbreviations

ANM: Age at Natural Menopause

BMI: Body Mass Index

CLSA: Canadian Longitudinal Study on Aging

CI: Confidence intervals

CVD: Cardiovascular disease

GD: Gestational Diabetes

HR: Hazard Ratio

HT: Hormone Therapy

NF- κB: Nuclear factor-kappaB

ROS: Reactive Oxygen Species

T1D: Type 1 Diabetes

T2D: Type 2 Diabetes

General Introduction

Biology of Menopause

The ovaries consist of a fixed number of follicles, that decline with age. Each follicle comprises of a primary oocyte (immature egg) which is surrounded by granulosa cells, and thecal cells. The number of follicles present in the ovaries are used to estimate the female's 'ovarian reserve'. Upon depletion of these follicles a female is said to have reached menopause. The clinical diagnosis can be made upon 12 consecutive months of amenorrhea.[1]

Importance of studying Age at Natural Menopause (ANM)

An important clinical milestone in a female's reproductive life is the onset of menopause. While it marks the end of one's reproductive years, it is also an important health transition. The age at which one reaches menopause can have important implications on the individual's health status. Early menopause is a risk factor for adverse health outcomes including osteoporosis, cardiovascular diseases, diabetes, neurological and psychiatric disturbances, and overall mortality[2,3], whereas later age at menopause has been found to increase risk of reproductive organ cancers including breast, endometrial, and ovarian cancers.[4] The average age of menopause can range anywhere between 46 to 52 years, however significant geographical and ethnicity-based differences exist.[5] For instance, women from South Asian, Middle Eastern, Southeast Asian, and African American/Black background have been found to reach menopause earlier than Caucasian women (from Europe and Australia), who in turn were more likely to reach menopause sooner than Japanese women.[6] Reaching menopause before the age of 40 years is defined as having 'premature menopause' or 'primary ovarian insufficiency' (POI), while reaching menopause between the ages of 40 and 45 years is denoted as having 'early

menopause'. Globally, 2% of women are known to experience POI, whereas 5-10% women experience early menopause.[7,8] The age range of late onset of menopause is less well-defined, while some studies have denoted ages at or above 55 years as 'late'[9], others used a threshold of 54 years or above[10], all while some use a threshold of 50 years[11]. Due to the ill-defined nature of late menopause, its epidemiology is also less well-defined.

Diabetes Mellitus

Diabetes mellitus is a chronic condition characterized by hyperglycemia (elevated glucose levels in the blood) where the body loses its ability to use or produce insulin. There are three major types of diabetes including type 1 diabetes (T1D) , type 2 diabetes (T2D), and gestational diabetes (GD).[12]

Type 1 Diabetes, Type 2 Diabetes, and Gestational Diabetes

T1D is marked by lack of insulin due to the destruction of the beta (β) cells of the pancreatic islets of Langerhans. This destruction is driven by an autoimmune reaction which leads to an absolute deficiency of insulin.[13] Therefore management of patients with T1D requires regular, and careful administration of exogenous insulin. The exact reasons of disease onset remain unknown, however, both genetics and environmental factors have been shown to play important roles.[13] Approximately, 9% of all diabetic cases are of T1D, making the overall prevalence in the general population close to 0.7%.[14,15] Furthermore, while most cases of T1D are diagnosed at younger ages, late onset T1D is also common with almost 30% of all T1D cases being diagnosed after the age of 30.[16] Specifically among adult onset autoimmune diabetes,

latent autoimmune diabetes of adulthood (LADA) accounts for 2-12% of all diabetes cases in adults making it the most prevalent type of adult onset T1D.[17,18]

T2D, on the other hand, is characterized by insensitivity of the body to insulin and was originally known as 'adult onset diabetes'. However, with rising obesity and physical inactivity levels around the globe, the incidence of T2D among youth and young adults has been steadily increasing.[19] T2D comprises of approximately 90% of all diabetic cases, making the overall prevalence in the general population approximately 7.3%.[14,15] Although being overweight or obese has been shown to be the biggest predictor of T2D, other predictors include poor diet, inactivity and smoking.[20]

Finally, GD is similar to T2D in presentation however as its name suggests, it presents exclusively during pregnancy. According to the American Diabetes Association a woman is considered gestational diabetic if she experiences glucose resistance for the first time during pregnancy.[21] Approximately 3-20% of all births in Canada are complicated by GD.[22]

Significance of thesis

As prevalence of diabetes continues to grow in Canada and across the world, it is essential that we try to understand the magnitude of its impact on the reproductive health of females. On average, females spend over a third of their life post menopause.[23] Provided that the events and health risks an individual is exposed to in early life can have tremendous impact on the health trajectories and quality of life of that person in later years, understanding how premenopausal diabetes impacts ANM is an crucial first step to understanding the long-term impact of diabetes on females' health.[24] Lack of well-designed studies and consensus among these studies are some of the issues facing this topic. This thesis aims to provide a clearer

perspective into the role of different types of diabetes on ANM through the means of a large sample, comprehensive adjustment of confounders, and strong statistical methods.

Abstract

Background: Diabetes is one of the most prevalent chronic conditions across the globe. With growing incidence of youth onset diabetes more women are expected to spend a larger proportion of their reproductive years with diabetes. It is important to understand the long-term implications of premenopausal diabetes on women's reproductive health including their age at natural menopause (ANM).

Objectives: The present study aims to use a large cohort of females to investigate the association between pre-menopausal type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes (GD) and ANM.

Methods: Baseline data from the Comprehensive Cohort of the Canadian Longitudinal Study on Aging was used for this analysis. Females who reported having premenopausal diagnosis of diabetes were considered exposed. Kaplan-Meier cumulative survivorship estimates and multivariable Cox regression models were used to assess the association between different types of diabetes and ANM. Various socio-demographic, lifestyle and premenopausal clinical factors were adjusted in the final model as covariates.

Results: The sample comprised of 11,436 participants, and was (weighted N= 1,480,323) Canadian females aged 45 to 85 years. Participants had a median ANM of 52 years. After adjusting for ethnicity, education, smoking, BMI and premenopausal conditions including hypertension among other covariates, early age of diagnosis of both T1D (<30 years) and T2D (30-39 years) was associated with earlier menopause (T1D<30: HR = 1.53, 95% CI 1.03-2.27 and T2D 30-39 : HR= 1.77, 95% CI 1.09-2.88) as compared with non-diabetics. Additionally, later age of diagnosis of T2D diabetes (>50 years) was associated with later age at natural menopause (T2D: HR= 0.39, 95% CI 0.27-0.55). No significant association between GD and ANM was noted.

Conclusion: This is one of the first studies reporting an association between early diagnosed T1D or T2D and early ANM. Our results support the literature showing accelerated ovarian aging among young diabetics. Growing incidence of youth-onset T2D warrants more research geared towards understanding the long-term health implications on women's reproductive health and aging.

Keywords: diabetes , menopause, Kaplan Meier curves, Cox proportional hazards model, CLSA

Introduction

Over the past few decades, the prevalence of diabetes has grown steadily across the globe among all age groups.[12] According to the World Health Organization, the number of people living with diabetes rose from 108 million in 1980 to 422 million in 2014.[12,25] While diabetes affects both males and females who share similar risk factors, the influence of these risk factors and the clinical impact of this chronic disease can differ significantly between the two sexes.[26,27] Evidence shows that women have higher BMI at diagnosis of diabetes as compared to men[28], additionally low socio-economic status, and lower levels of education attainment are associated with greater risk of Type 2 diabetes (T2D) among women than in men.[29–31] The clinical impact of diabetes among the two sexes has also been noted to be different. The Stockholm Heart Epidemiology Program (SHEEP) study found diabetic women to have sevenfold greater risk of developing cardiovascular diseases as compared to a threefold risk in men.[32] This increased cardiovascular risk has also been shown to translate to greater cardiovascular mortality among women as compared to men [33]. According to the International Diabetes Federation (IDF), 222.9 million women aged 20 years and older lived with diabetes worldwide in 2019.[25] With growing prevalence among all age groups, and increasing incidence of youth-onset diabetes, more women are expected to spend a greater portion of their reproductive years with diabetes.[34–36] Having said that, it is important to understand the long term implications of premenopausal diabetes on women's health, including their reproductive health.

One indicator of a woman's reproductive health is their age at natural menopause (ANM), defined as the age at which a woman experiences 12 consecutive months of amenorrhea.[8] The average age of menopause can range anywhere between 46 to 52 years.[37] Although every female will go through menopause at some point in their lives, the age at which one reaches menopause can impact one's future health outcomes. Early ANM has been

associated with negative health outcomes that include greater risk for cardiovascular diseases [38], fractures [39], and all-cause mortality.[9] The incidence of T2D post early menopause is also well established. In fact, a recent prospective cohort that followed postmenopausal women for 9 years reported a hazard ratio for T2D of 2.4 (95% CI 1.3, 4.3) among women with early menopause as compared to those who reached menopause after 55 years. [40]

While most studies have looked at the association between ANM and diabetes cross-sectionally or have studied the risk of developing diabetes upon reaching menopause, few studies have examined the inverse - the role of pre-menopausal diabetes, and its association with ANM. Furthermore, amongst the studies that have examined this relationship some have been limited by small sample size[41–43], whereas others adjust only for limited number of confounding variables such as age, parity, and smoking history, while failing to include other important sociodemographic, behavioral and clinical variables.[44] Consequently, the association between pre-menopausal diabetes and ANM remains debated. Some studies show no association [42,44,45], while others conclude a significant reduction in ANM.[46,47] In addition, some highlight that the association between the two might in fact be dependent on time of diagnosis of diabetes.[48]

The association between gestational diabetes (GD) and ANM has also been highly overlooked. GD is defined as the onset of diabetes or hyperglycemia during pregnancy. Recent large cohort based studies have shown history of GD to be a strong predictor of long-term cardiovascular disease.[49] Given that premenopausal cardiovascular disease is risk factor for early ANM [10], it is then important to explore if GD is an independent predictor of ANM. A recent study presented at the North American Menopause Society in the United States found that women with a history of diabetes and hypertension during pregnancy were more likely to experience heightened menopausal transition symptoms such as hot flashes, than those without

diabetes and hypertension during pregnancy.[50] This highlights the importance of studying the long term health outcomes among those with a history of GD and hypertension. As per the authors' knowledge no study has examined the association between GD and ANM to date. The present study aimed to use a large cohort of females to investigate the association between pre-menopausal T1D, T2D and GD and ANM.

Methods

Study Design

The Canadian Longitudinal Study on Aging (CLSA) is a national, longitudinal study of over 50,000 Canadian men and women aged 45 to 85 years when recruited at baseline.[51] The study was initiated in 2010 and baseline data was collected between 2010 and 2015. The main aim of CLSA is to understand the complex process of aging through the examination of various intrinsic and extrinsic factors associated with mid to older aged individuals over a 20-year period. The study has two cohorts of participants: (1) the Tracking cohort comprising of 21,241 individuals and (2) the Comprehensive cohort comprising of 30,097 individuals. While the two groups do share some core survey components, they differ in their sampling strategy, data collection and in the scope of information collected. More information is available at https://clsa-elcv.ca/doc/511.

The present study is based on the data collected at baseline from the Comprehensive cohort. This cohort sampled participants from a 25-50 km radius of the 11 data collection sites located across seven provinces at baseline. These participants were administered an in-home questionnaire and were asked to visit a data collection site near them for in-depth physical assessments and health measures. The cohort included 15,320 females and 14,777 males for a total of 30,097 participants. Those living on First Nations reserves or settlements, full-time members of the Canadian Armed Forces and non-English or non-French speakers were excluded from the survey. Additionally those living in long-term institutions or with cognitive impairment (as determined by trained CLSA interviewers) were also excluded.

Study participants and exclusions

The original sample was comprised of 15,320 women. Additional exclusions were applied for the present study that have been summarized in Figure 1. Women who underwent surgical removal of the uterus and/or ovaries via a hysterectomy (16.3% of the overall sample), indicated

having breast, ovarian or other female genital organ cancers (8.1% of the overall sample) were excluded. Additionally, those who failed to report their menopause status (0.7% of the overall sample), age of menopause onset (2.0 % of the overall sample), diabetes status and age of diagnosis (0.3% of the overall sample) were considered missing and excluded from the final analysis. After these exclusions (25.4% of the overall sample) 11,436 women remained for the analysis.

Outcome Assessment (ANM)

Menopausal status and ANM were collected via the baseline at-home questionnaire and required participants to retrospectively recall their age at which they had their last menstrual period. Menopausal status was assessed using the question " Have you gone through menopause, meaning that your menstrual periods stopped for at least one year and did not restart?" Those who responded with "Yes" were considered as having reached menopause naturally. The ANM was ascertained based on the response to the question, "How old were you when your menstrual periods stopped for at least one year and did not re-start?", which was coded as age (in years) and was treated as a continuous variable.

Exposure Assessment (Premenopausal Diabetes)

The presence of diabetes and the date of diagnosis was self-reported and was assessed by the baseline questionnaire conducted at the CLSA data collection site. The main diabetes variable was defined using the type of diabetes and age of diagnosis, and was categorized as GD, T1D <30 years , T1D >30 years, T2D <30 years, T2D 30-39 years, T2D 40-49 years, and T2D ≥ 50 years.

The questionnaire first asked participants to report the type of diabetes they were diagnosed with. The options included were 'Type 1', 'Type 2' or 'Neither'. Participants were

then asked to report their age at first diagnosis. Females who were diagnosed with diabetes before reaching menopause were considered exposed, and categorized as T1D or T2D in the final diabetes variable. Moreover, women who reported being diagnosed with diabetes during or after the year of their menopause were included in the reference category, 'No Diabetes' along with those who reported never having diabetes.

Moving forward, participants were also asked the question "When you were pregnant, did the doctor tell you that you had diabetes, borderline diabetes or high blood sugar?". However, the date of GD diagnosis was not obtained. So, among participants who reported having either T1D or T2D and also reported experiencing GD, the chronological order of the two diagnoses could not be ascertained. Therefore, the subset of women who reported having both 'premenopausal T1D and GD' or 'premenopausal T2D and GD' were categorized as T1 or T2 diabetics, respectively. Whereas, those who reported only having diabetes during pregnancy were categorized as having 'GD'.

Covariates

Sociodemographic variables included ethnicity (categorized as white only, Indigenous, and mixed/other), marital status (categorized as partner, and no partner), education (categorized as high-school or less, any college diploma or certificate, bachelor's degree, and higher than bachelor's degree) and household income (categorized as <20,000 , 20,000-50,000 , 50,000-100,000 , and >100,000).

Lifestyle factors included alcohol use (categorized as never, drink less than weekly, and drink at least weekly), smoking (categorized as current, former, and never), physical activity which was based on whether the participants met Canadian guidelines[52] (150 min of moderate-vigorous physical activity per week), and BMI which was calculated using the participants height

and weight. The cut-off for under-weight individuals was increased to 20.0 kg/m^2 because most females included in this study were aged 45 years and older therefore very few participants were under 18.5 kg/m^2. Similar approach has been used by other studies utilizing older aged sample.[53]

Premenopausal clinical factors included nulligravidity (ever being pregnant) and health conditions such as cardiovascular diseases (including stroke, mini-stroke angina and heart attack), hypertension, osteoporosis, corticosteroid use, depression, hypothyroidism and hyperthyroidism. All of these were ascertained to be diagnosed before menopause and were categorized as Yes and No.

Statistical Analysis

Survival Analysis was used to allow participants who had not yet reached menopause to be included as censored observations. The endpoint was defined as the ANM for post-menopausal, and age at interview for non-menopausal females and age at initiation of hormone therapy (HT) for females using HT before menopause. Kaplan Meir estimate were used to ascertain the median ANM for females with different types of diabetes and covariates. Finally, Cox proportional hazard regression models were used to estimate the association between the exposure variables and ANM. Hazard Ratios (HRs) along with their 95% confidence intervals were reported. Two different models were used, with the first model reporting independent association between the exposure variables and ANM, and the second model adjusting for all the covariates. HRs greater than 1 indicate early menopause, whereas less than 1 indicate later menopause in comparison to the reference value. In addition, given the close association between adiposity, hypertension and diabetes, interaction between diabetes and hypertension as well as diabetes and BMI was also tested. This was done by including interaction terms in the final adjusted model. Finally, sensitivity analysis was conducted to ensure that those with premature

menopause were not skewing the HRs towards early menopause. To do this, those reporting premature menopause were excluded from the analysis. The proportional hazard assumption was checked using log-log plots of survival probabilities over time by applicable factor variables, and through visualizing plots of scaled Schoenfeld residuals versus predictors. These did not indicate violation of the assumption. Statistical significance for all analyses was set at alpha < 0.05. All statistical analyses were performed in STATA Statistical Software, version 13, (StataCorp, College Station, TX).

Results

Table 1 summarizes the descriptive statistics of the sample comprising of 11,436 (weighted N = 1,474,412). The mean age at interview was 61.4 years (SD = 10.0). Natural menopause was reported by 53.0% of the participants (weighted = 784,127). The median ANM of the sample was 52 years (interquartile range, IQR: 50-55). In the overall sample, 6.7% of the sample reported having GD (weighted N = 97,623), 0.3% reported having premenopausal T1D (weighted N = 5,138), and 2.0% reported having premenopausal T2D (weighted N = 28,626). Additionally, majority of the participants included were White (93.6%), and over 70% had a partner (71.8%). Approximately 75% of the participants had a college diploma or higher, and almost 40% had an income of $100,000 or higher. A large proportion of the sample were former smokers (54.9%), while 36.4% reported never smoking. Over 50% of participants reported drinking weekly (56.8%), whereas close to 60% did not meet Canadian physical activity guidelines. Clinically, close to 85% of the participants reported being pregnant at least once, 13.0% reported having premenopausal hypertension, 16.4% reported experiencing depression before menopause, and 11.5% reported having premenopausal hypothyroidism.

Figure 2 illustrates the survival curves based on participants' diabetic status. The crude median ANM among non-diabetics was 52 years (IQR: 50-55), whereas the crude median ANM among all diabetic participants combined was 53 years (IQR: 50-55). The median ANM among diabetic participants changed once participants was stratified based on type and age of diagnosis. While those diagnosed with both GD and T1D<30 years had the same crude median ANM of 52 years (IQR: 50-55), the median ANM among T1D >=30 years was 51 years (IQR: 49-53). Among T2 diabetics, the highest crude median ANM of 56 years (IQR: 54 to 65) was noted for T2D over 50 years at diagnosis, whereas the lowest median ANM of 51 years (IQR: 46-53) was noted among T2D aged 30-39 years.

Table 2 displays the results of the unadjusted and the adjusted Cox regression analysis. After adjusting for socio-demographic, lifestyle, and clinical factors, females diagnosed with T1D before the age of 30 were significantly more likely to reach menopause earlier (HR=1.55; 95% CI: 1.05-2.29) as compared to non-diabetics. Similarly, participants diagnosed with premenopausal T2D between the ages of 30-39 years were more likely to reach menopause earlier (HR= 1.81; 95% CI: 1.12- 2.94), however those diagnosed with premenopausal T2D after the age of 50 were more likely to reach menopause later, as compared to their non-diabetic counterparts (HR: 0.39 ; 95% CI: 0.27-0.56). The association between GD and ANM was not found to be significant. Additionally, females with lower levels of education, lower household income, as well as current and former smokers were more likely to reach menopause earlier. Whereas consuming alcohol, ever being pregnant, having premenopausal hypertension, osteoporosis, and depression were some factors associated with late ANM. Interactions between BMI, hypertension and the main diabetes variable was tested, however no significance was found.

Upon the exclusion of premature menopause cases (n = 320) from the analysis, the relationship between early diagnosis of T1D and T2D, and early menopause, as well as the relationship between late T2D diagnosis and late menopause remained significant (Table 3).

Discussion

This large retrospective cohort study found that females who had experienced T1D before the age of 30 were significantly more likely to reach menopause earlier, as compared to their non-diabetic counterparts. In addition, participants diagnosed with T2D early on (between the ages of 30-39 years) were significantly more likely to reach menopause earlier, whereas those reporting later ages of T2D diagnosis (>= 50) reached menopause at a later age. The association between GD and ANM was not significant. As per the best knowledge of the authors this is one of the first studies to separately examine the association between age of diagnosis among T1D and T2D with ANM, as well as the first to explore the relationship between GD and ANM.

The association between early diagnosis of diabetes and early ANM, and late diagnosis of diabetes and late ANM has been shown previously by Brand et al. (2014).[48] Their study which was based on a large cohort of women from the European Prospective Investigation into Cancer and Nutrition (EPIC) reported an age of diagnosis related association with ANM. The study found that individuals diagnosed with diabetes before the age of 20 reached menopause earlier, whereas those diagnosed after the age of 50 reached menopause later than their non-diabetic counterparts. However, their study failed to differentiate between different types of diabetes and it was assumed that those diagnosed at younger ages (<20 years) were most likely T1 diabetics, whereas those diagnosed at later ages (>50 years) were T2 diabetics. The present study adds on to these findings by showing that early diagnosis of both T1D (diagnosed prior to age 30) and T2D (diagnosed between ages 30-39) can act as drivers to early menopause, as well as confirms the speculation that diagnosis of T2D at later ages is related to later ANM.

Moreover, this study is in line with other studies that have individually assessed the association between specific diagnosis of diabetes (T1D or T2D) and ANM. Firstly, the results of the present study are in agreement with the observations noted by Dorman et al. (2001), where

the association between T1D and early menopause was first reported.[43] Their study reported an increase in age at menarche and a 6 year reduction in ANM among T1 diabetics when compared with non-diabetic sisters or healthy controls. [43] Having said that, there are some studies that have evaluated this relationship and found no significant association, including a study conducted among Finnish females[42], and a more recent study conducted among Dutch females[44]. However, it should be noted that the latter failed to adjust for important covariates such as education, physical activity and BMI, which may have led to incomplete evaluation of the association. In regards to T2D, our results showed agreement with a large multinational Latin-American study that found women diagnosed with T2D before the age of 45 to have a three-fold greater risk of reaching menopause early as compared to their non-diabetic counterparts.[47] Alternatively, our results differed from an earlier study comprising of Mexican females that reported no association between T2D and ANM.[41] Nevertheless their exclusion criteria excluded females who had other metabolic conditions which may have biased their study population to include healthier T2 diabetics, and dampened the association between T2D and menopause.

Finally, although the association between GD and ANM was not significant in the present analysis, there is still merit in further examining this relationship in future studies. Due to the limitations placed by the survey questionnaire utilized for the current study, the females included in the 'GD' category were a subset of those who did not report developing other types of diabetes before menopause. However, given the high likelihood of developing T2D 5-10 years post experiencing GD[54], it is possible that some participants were misclassified as T2D when in fact they might have developed GD prior to T2D diagnosis. A study conducted by Tobias et al. (2017) among a large cohort of American women reported that a history of GD significantly increased the risk of long-term CVD among women as compared to those without GD. [49]

Additionally it was also found that the risk of developing long-term CVD among those with both GD and T2D was close to 4 times (HR: 3.71; 95% CI, 1.79-7.67) when compared to women without GD or T2D, however this association was no longer statistically significant among women who only had GD.[49] This finding, along with the findings from our study support the assumption that there is lower risk of long-term health complications among females with GD only as compared to those with both GD and T2D. However, given the increased health risk noted among patients with both GD and T2D in other studies, it is important that the relationship between GD and ANM be further evaluated in future studies.

Several underlying factors might be regulating the relationship indicated in our study between long-term diabetes, and ANM. While presence of autoimmune ovarian antibodies among T1 diabetics could be hypothesized to be leading to earlier ANM, evidence suggests that poorly controlled diabetes can have detrimental effects on multiple organ systems in the body including reproductive organs, and overall reproductive health.[55] Additionally, lack of insulin in animal models of T1D has also been shown to lead to impaired oocyte maturation, anovulation and follicular apoptosis.[56] It is then possible that a combination of glucose toxicity, and low levels of circulating insulin in T1D, and advanced stages of T2D might be leading to hastened deterioration of the ovarian reserve, and follicles. Having said that, the reasoning behind later ANM among those diagnosed later with T2D remains unclear and warrants more research.

The present study confirmed some well-known associations seen between smoking, education and clinical factors. The association noted in the present study between both former and current smokers, and earlier menopause has been shown by multiple studies. [5,48,53,57] Moreover, the association seen between lower socio-demographic, and economic factors such as lower levels of income and education, and early menopause is also well established, and was

corroborated by the results of the current study.[5,48,58] Among clinical factors, ever being pregnant, and premenopausal depression were both found to be significantly associated with later menopause, both of which are in line with the literature. [45,48,59] Interestingly premenopausal hypertension was found to be a significant predictor of later ANM. The relationship between hypertensive disorders and ANM remains debated in the literature. While some studies have found no association between hypertension and ANM[59], others have indicated earlier ANM among hypertensive females[60], whereas some others have reported similar trend to those reported in our study.[45] Having said that, this relationship might have been modulated by the age of diagnosis of hypertension. A pooled analysis of over 170,000 women found that women diagnosed with cardiovascular diseases before the age of 35 were significantly more likely to reach menopause earlier, however no association was found between hypertension and ANM among women diagnosed after the age of 35.[38] Given that over 75% of the participants in the present study were diagnosed with premenopausal hypertension after the age of 35, it is possible that the relationship between premenopausal hypertension and ANM is mediated by age of diagnosis, similar to the trend seen in diabetes. Finally, some novel associations were found between premenopausal hypothyroidism, and premenopausal corticosteroid use, both of which were associated with later ANM. Given that hypothyroidism is an autoimmune disease, we had predicted earlier menopause among these cases. Nevertheless, as per our knowledge both these clinical factors have not been studied in relation to ANM, therefore further research is warranted.

Strengths and Limitations

This study has many strengths. As per our knowledge this is the first study to examine the relationship between GD and ANM. Additionally, the large sample size and careful adjustment of important socio-demographic, lifestyle and clinical covariates allowed for a more accurate and well-rounded study. Adjustment of premenopausal health conditions including diabetes diagnosis permitted clarity of temporal sequence of events, and their impact on the outcome. Finally, the inclusion of specific diagnosis of diabetes (T1D, T2D and GD) as well as age of diagnosis allowed us to understand the impact of both the type of diabetes, and length of disease on ANM. Having said that, there are certain limitations to our study. First, due to the nature of the questionnaire it is possible that some participants with GD were misclassified as T1 diabetics or T2 diabetics. Additionally, assessment of both diabetes and ANM was based on self-report, and not confirmed using medical records which could have led to misclassification of the both exposure and outcome. Having said that, self-reported ANM has been shown in previous studies to have acceptable validity and reliability.[61,62] Finally, important covariates such as oral contraceptive use, age at menarche, parity, and breastfeeding were not included in this analysis as this information was not included in CLSA.

Conclusion

Overall the present study found females with early diagnosis of T1D or T2D reported earlier ANM whereas those with later age of diagnosis of T2D reported later ANM, as compared to their non-diabetic counterparts. These associations persisted after adjusting for various socio-demographic, lifestyle and premenopausal clinical factors. In light of increasing prevalence of T2D among younger individuals more studies examining this relationship are required. Furthermore, studies understanding the underlying mechanisms of this association are warranted.

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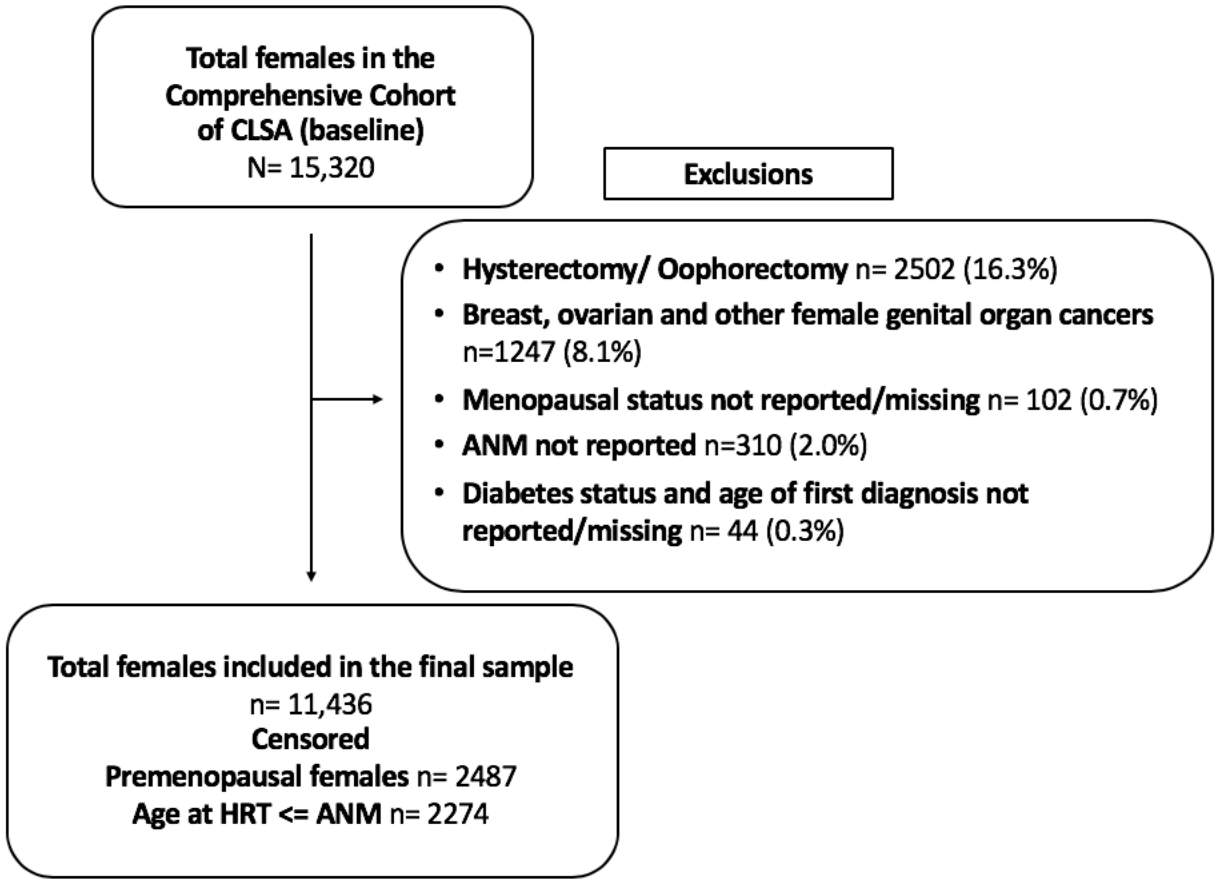

Figure 1: Participant flowchart, Canadian Longitudinal Study on Aging (CLSA).
ANM: Age at Natural Menopause ; CLSA: Canadian Longitudinal Study on Aging ; HRT: Hormone Replacement Therapy

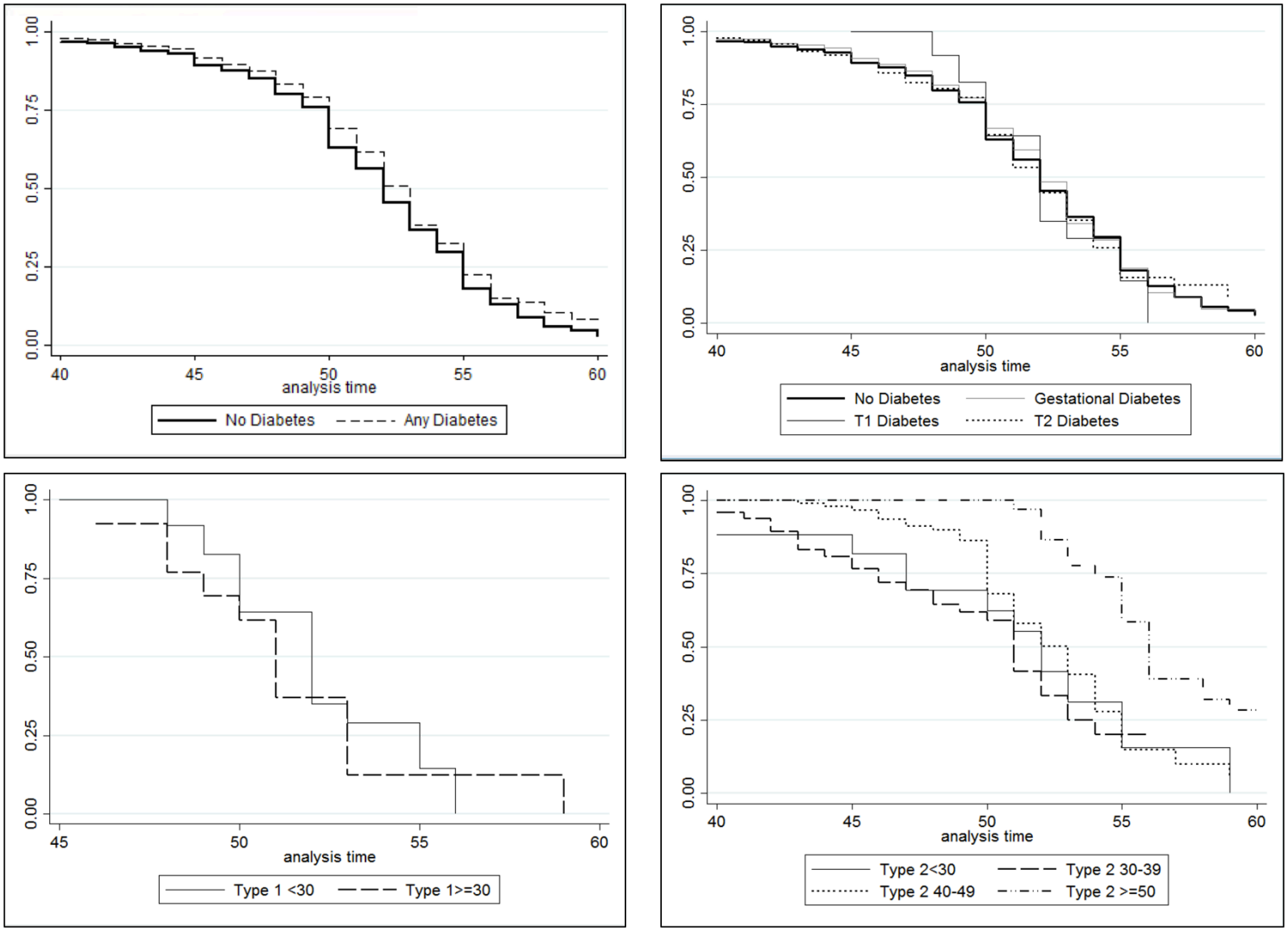

Figure 2: Kaplan Meier curves stratified by diabetes status and age. Type 1: Type 1 Diabetics ; Type 2: Type 2 Diabetics

Table 1: Baseline characteristics of the study population from the Canadian Longitudinal Study on Aging, enrolled between 2010 and 2015.

Variables	Total Sample N (%)*	Non-censored cases %**	Median ANM (IQR)***
Diabetes			
No Diabetes	1336779 (91.1)	53.9	52 (50-55)
GD	97623 (6.7)	45.5	52 (50-55)
Type 1:	5138 (0.3)		
T1D <30 years	3376 (0.2)	52.5	52 (50-55)
T1D >= 30 years	1762 (0.1)	72.6	51 (49-53)
Type 2:	28626 (2.0)		
T2D <30 years	1908 (0.1)	73.1	52 (47-55)
T2D 30-39 years	5872 (0.4)	55.2	51 (46-53)
T2D 40-49 years	13946 (1.0)	51.3	53 (50-55)
T2D >= 50 years	6900 (0.5)	40.9	56 (54-65)
Sociodemographic Variables			
Ethnicity			
White	1379148 (93.6)	53.5	52 (50-55)
Indigenous	17389 (1.2)	51.9	53 (49-56)
Mixed and other backgrounds	77070 (5.2)	49.8	52 (49-55)
Marital Status			
Partner	1057650 (71.8)	50.8	52 (50-55)
No Partner	416016 (28.2)	59.8	52 (49-55)
Education			
Higher than bachelor's degree	289160 (19.6)	50.6	52 (50-55)
Bachelor's Degree	311119 (21.1)	61.8	52 (48-55)
Any college diploma or certificate	496229 (33.7)	52.5	52 (49-55)
High-school or less	377440 (25.6)	49.7	52 (50-55)
Household Income (CAD)			
>100,000	561181 (40.7)	44.6	53 (50-55)
50,000-100,000	468891 (34.0)	56.0	52 (50-55)
20,000-50,000	280728 (20.4)	63.4	52 (48-55)
<20,000	66670 (4.8)	61.4	51 (48-55)
Lifestyle Factors			
Alcohol Use			
Never	165853 (11.6)	57.9	52 (48-55)
Drink less than weekly	454481 (31.7)	53.7	52 (49-55)
Drink at least weekly	815625 (56.8)	52.1	52 (50-55)
Smoking			
Never	535835 (36.4)	51.1	52 (50-55)
Former	807137 (54.9)	54.0	52 (50-55)
Current	128294 (8.7)	57.4	51 (48-54)
Physical Activity			
Does not meet Canadian guidelines	841698 (59.4)	55.1	52 (50-55)
Meets Canadian guidelines	575063 (40.6)	50.3	52 (50-55)
BMI (kg/m^2)			
20.0-24.99 (normal weight)	537865 (36.5)	50.4	52 (50-52)
<20.00 (underweight)	69002 (4.7)	48.3	52 (49-55)
25.0-29.99 (overweight)	494518 (33.5)	54.5	52 (50-55)
>30.0 (obese)	373026 (25.3)	56.4	52 (49-55)
Premenopausal Clinical Factors			
Ever been pregnant			
No	224347 (15.3)	55.2	52 (49-55)
Yes	1245816 (84.7)	52.9	52 (50-55)
Premenopausal CVD (incl: stroke, heart attack, angina)			
No	1447107 (98.3)	53.4	52 (50-55)
Yes	25026 (1.7)	48.3	53 (50-57)
Premenopausal Hypertension			
No	1273234 (87.1)	54.0	52 (49-55)
Yes	189413 (13.0)	48.8	54 (51-56)
Premenopausal Osteoporosis			
No	1431291 (98.1)	53.3	52 (50-55)
Yes	28465 (2.0)	50.6	53 (51-57)
Premenopausal use of corticosteroids			
Never	1335246 (92.6)	54.6	52 (50-55)
Ever	107172 (7.4)	36.9	53 (51-56)
Premenopausal Depression			
No	1226629 (83.6)	54.6	52 (50-55)
Yes	239929 (16.4)	45.9	53 (50-55)
Premenopausal Hypothyroidism			
No	1286942 (88.5)	53.8	52 (50-55)
Yes	167723 (11.5)	48.0	53 (50-55)
Premenopausal Hyperthyroidism			
No	1418898 (97.4)	53.3	52 (50-55)
Yes	38325 (2.6)	51.5	52 (50-55)

Abbreviations: ANM: Age at Natural Menopause ; BMI: Body Mass Index ; CI: Confidence Interval ; CVD: Cardiovascular disease including stroke, heart attack and angina ; GD: Gestational diabetes ; IQR: Interquartile Range ; T1D: Type 1 diabetes ; T2D: Type 2 diabetes
* Estimated using inflation weights
** Estimated using analytic weights
*** Calculated using Kaplan-Meier estimate

Table 2: Unadjusted and Adjusted Hazard Ratios

Variables	Unadjusted	Adjusted
	HR (95% CI)	HR (95% CI)
Diabetes		
No Diabetes	1	1
GD	0.94 (0.84-1.05)	0.97 (0.86-1.11)
Type 1:		
T1D <30 years	0.95 (0.58-1.55)	**1.55 (1.05-2.29)**
T1D >= 30 years	1.24 (0.70-2.20)	0.70 (0.35-1.41)
Type 2:		
T2D <30 years	1.12 (0.65-1.93)	1.37 (0.66-2.87)
T2D 30-39 years	1.44 (0.91-2.28)	**1.81 (1.12-2.94)**
T2D 40-49 years	0.91 (0.70-1.18)	0.93 (0.72-1.19)
T2D >= 50 years	**0.33 (0.24-0.45)**	**0.39 (0.27-0.56)**
Sociodemographic Variables		
Ethnicity		
White (Ref)	1	1
Indigenous	1.02 (0.82-1.28)	0.99 (0.76-1.30)
Mixed and other backgrounds	1.07 (0.94-1.22)	1.04 (0.89-1.21)
Marital Status		
Partner (Ref)	1	1
No Partner	**1.17 (1.11-1.23)**	1.04 (0.98-1.12)
Education		
Higher than bachelor's degree (Ref)	1	1
Bachelor's Degree	**1.23 (1.14-1.33)**	**1.12 (1.03-1.23)**
Any college diploma or certificate	**1.09 (1.01-1.17)**	1.02 (0.94-1.11)
High-school or less	1.06 (0.98-1.14)	1.07 (0.98-1.16)
Household Income (CAD)		
>100,000 (Ref)	1	1
50,000-100,000	**1.19 (1.11-1.26)**	**1.14 (1.06-1.22)**
20,000-50,000	**1.32 (1.24-1.42)**	**1.23 (1.12-1.34)**
<20,000	**1.39 (1.23-1.56)**	**1.20 (1.04-1.39)**
Lifestyle Factors		
Alcohol Use		
Never (Ref)	1	1
Drink less than weekly	0.92 (0.85-1.00)	**0.90 (0.82-0.99)**
Drink at least weekly	0.87 (0.80-0.94)	**0.87 (0.79-0.95)**
Smoking		
Never (Ref)	1	1
Former	**1.06 (1.00-1.11)**	**1.12 (1.05-1.19)**
Current	**1.53 (1.39-1.70)**	**1.55 (1.38-1.74)**
Physical Activity		
Does not meet Canadian guidelines (Ref)	1	1
Meets Canadian guidelines	**0.92 (0.88 – 0.97)**	0.97 (0.91-1.02)
BMI (kg/m^2)		
20.0-24.99 (normal weight) (Ref)	1	1
<20.00 (underweight)	1.05 (0.91-1.20)	1.01 (0.86-1.18)
25.0-29.99 (overweight)	1.02 (0.97-1.09)	1.04 (0.97-1.11)
>30.0 (obese)	1.00 (0.94-1.07)	1.05 (0.97-1.13)
Premenopausal Clinical Factors		
Ever been pregnant		
No (Ref)	1	1
Yes	**0.85 (0.80-0.91)**	**0.83 (0.77-0.90)**
Premenopausal CVD (incl: stroke, heart attack, angina)		
No (Ref)	1	1
Yes	**0.69 (0.56-0.84)**	0.80 (0.63-1.01)
Premenopausal Hypertension		
No (Ref)	1	1
Yes	**0.68 (0.63-0.73)**	**0.67 (0.62-0.73)**
Premenopausal Osteoporosis		
No (Ref)	1	1
Yes	**0.67 (0.56-0.80)**	**0.67 (0.55-0.81)**
Premenopausal use of corticosteroids		
Never (ref)	1	1
Ever	**0.68 (0.61-0.75)**	**0.69 (0.61-0.78)**
Premenopausal Depression		
No (Ref)	1	1
Yes	**0.86 (0.80-0.92)**	**0.85 (0.78-0.92)**
Premenopausal Hypothyroidism		
No (Ref)	1	1
Yes	**0.81 (0.74-0.87)**	**0.83 (0.76-0.91)**
Premenopausal Hyperthyroidism		
No (Ref)	1	1
Yes	0.95 (0.81-1.12)	1.05 (0.86-1.27)

Abbreviations: BMI: Body Mass Index ; CI: Confidence Interval ; CVD: Cardiovascular disease including stroke, heart attack and angina ; GD: Gestational diabetes ; HR: Hazard Raito ; T1D: Type 1 diabetes ; T2D: Type 2 diabetes

Table 3: Sensitivity analysis after excluding premature menopause cases

Variables	After Premature Menopause cases were removed HR (95% CI)
Diabetes	
No Diabetes	1
GD	0.97 (0.85-1.11)
Type 1:	
T1D <30 years	**1.59 (1.07-2.36)**
T1D >= 30 years	0.72 (0.35-1.45)
Type 2:	
T2D <30 years	1.30 (0.62-2.74)
T2D 30-39 years	**1.78 (1.08-2.93)**
T2D 40-49 years	0.96 (0.75-1.24)
T2D >= 50 years	**0.40 (0.28-0.57)**

Final model adjusted for sociodemographic variables (including ethnicity, marital status, education and household income), lifestyle factors (including alcohol use, smoking, physical activity and BMI) and premenopausal clinical factors (including ever being pregnant, premenopausal cardiovascular diseases, premenopausal hypertension, premenopausal osteoporosis, premenopausal corticosteroid use, premenopausal depression, premenopausal hypothyroidism and premenopausal hyperthyroidism).

Abbreviations: BMI: Body Mass Index ; CI: Confidence Interval ; CVD: Cardiovascular disease including stroke, heart attack and angina ; GD: Gestational diabetes ; HR: Hazard Raito ; T1D: Type 1 diabetes ; T2D: Type 2 diabetes

General Discussion

This thesis examined the association between premenopausal type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes (GD), and their association with age at natural menopause (ANM). Data from the Canadian Longitudinal Study on Aging of 11, 436 Canadian females was used to carry out the analysis. The median age at ANM was 52 years (IQR: 50-55) for the overall sample. After adjusting for sociodemographic variables, lifestyle factors and premenopausal health conditions, a significant association was found between early diagnosed T1D, early diagnosed T2D and early ANM as compared to non-diabetics. Moreover, females diagnosed with T2D in later ages were significantly more likely to reach menopause later than their non-diabetic counterparts. Overall no significant association was found between GD and ANM.

Multiple biological factors are likely at play in the associations noted above. However, given the high complexity of the female reproductive system it is not surprising that the true effect of many of these agents and their metabolic pathways remain largely unknown. Below is a summary of some hormones that can be modulated by the presence of hyperglycemia or poor metabolic status, and have been seen to play an important role in determining ANM.

Anti-Mullerian Hormone (AMH)

AMH is a glycoprotein produced by the granulosa cells of the primary follicles in the ovary. Over the past few years AMH has become a reliable predictor for a female's ovarian reserve, which signifies the quality and quantity of a female's eggs. Low AMH levels in women with similar ages have been shown to be indicative of early menopause.[63–65] Although novel, there is some evidence to suggest that Type 1 diabetes might be associated with lower levels of

AMH. A study by Kim et al. (2016) found Type 1 diabetics aged less than 35 years of age had lower levels of AMH as compared to those with no diabetes.[66] Similar results were also reported by Soto et al. (2009) where Chilean women with Type 1 diabetes between the ages of 33 to 45 years were found to have significantly lower levels of AMH as compared to their non-diabetic counterparts.[67] The reasoning for differences in age groups between the two studies could be related to sample size differences. The study by Kim et al. (2016) utilized a much larger sample size than Soto et al. (2009) which may have led to more precise results in the former study. Given that AMH is produced by the granulosa cells in the follicles of the ovaries, lower levels of AMH have been predicted to be an outcome of granulosa cell injury. Nuclear factor-kappaB (NF- κB) is a protein complex which has been shown to be associated with inflammation and fibrosis of tissues is hypothesized to be causing this damage. A study conducted by Erbas et. al. (2014) on female diabetic rats models found that NF-κB levels were significantly higher in diabetic rats' ovaries as compared to controls.[68] Additionally, the number of primordial and primary follicles was also significantly lower in diabetic rats as compared to controls.[68] Both these observations were made along with a decline in AMH levels in these models. Having said that, production of reactive oxygen species (ROS) under hyperglycemic states has been found to upregulate NF- κB levels, thus making the ROS signaling pathway an important medical target.[69]

Kisspeptin

Kisspeptin is primarily known for its function in the brain where it stimulates the hypothalamus, and plays a role in gonadotropin releasing hormone (GnRH) secretion, thereby impacting the pituitary, and the subsequent release of gonadotropins (FSH and LH).[70] Over the last 2 decades, Kisspeptin has gained a lot of traction in the scientific community. While its

original role was of a tumor suppressor, it is now also known for its vital role in the onset of puberty and fertility. Recent studies in rodent models have revealed that kisspeptin is also expressed in peripheral tissues including the liver and pancreas where it has been shown to play an important role in energy balance and metabolism .[70,71] Moreover, glucagon (a hormone found in high concentrations in early stages of T2D) has been shown to further increase kisspeptin production in the liver.[72,73] Given that peripheral kisspeptin has been found to cross the blood-brain barrier[74] and increase GnRH secretion in animal models[75], it is then hypothesized that increased peripheral kisspeptin, increases FSH and LH production via its action on GnRH. This in-turn might lead to consistent, and long term follicle stimulation in T2 diabetic women, eventually causing earlier depletion of ovarian follicles. Furthermore, kisspeptin has also been found in ovaries, where sharp increase in its levels have been detected before ovulation.[76] Given Kisspeptin's close association with insulin, glucagon and ovulation, as well as its influence on multiple biological pathways makes it an important candidate for research.

Future Research Directions

First, further research is needed to understand the long-term effects of GD on ANM. Stratification by T2 diabetic status should be conducted to understand the differences in risk among those with GD only, and among those with both GD and T2D. Additionally, given the important role of BMI, physical activity, and quality of diet on diabetes management, changes in these lifestyle factors should be evaluated in relation to ANM. It would be interesting to know if proper weight management through physical activity, and diet control alleviate the risks of early ANM among early diabetics. Role of long term glucose management, and medications should also be assessed in relation to menopause symptoms and age of onset. Doing so may provide

greater insight into the role of diabetes medical therapies on ANM. Moreover, as diabetes incidence continues to grow, understanding the role of insulin and hyperglycemia on hormones such as Kisspeptin and AMH has never been more crucial, and therefore should be explored. Finally, it is important to highlight that there is a paucity of this research on ethnically diverse groups, which is ironical given the disproportionate burden of chronic disease such as diabetes on such populations.[77,78] It is therefore important that longitudinal studies exert greater efforts to include racially diverse populations, in order for medical research to be generalizable and inclusive. [79]

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