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RESEARCH ARTICLE

RELATION BETWEEN AGE AT MENOPAUSE, REPRODUCTIVE LIFE SPAN AND TYPE 2 DIABETES.

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Abstract

Background: The aims of this study are to (1) shed light on the temporal relation between development of menopause and development of type 2 diabetes. (2) Clarify whether early menopause and short reproductive life span could be considered as novel risk factor for type 2 diabetes. (3) Decide whether type 2 diabetes is to be considered a cause and/or a sequel of early menopause and short reproductive life span.

Subjects and Methods: This study was conducted on four hundred postmenopausal women. Their ages' range was (40-87y) with average mean (59.28±9.01y), a questionnaire was done to every subject including reproductive factors, baseline characteristics, and laboratory investigations.

Results: our study was on postmenopausal women. Their ages at menopause were (31-63) with mean average (47.73±5.02). The prevalence of diabetes in postmenopausal women was 38%. There was a significant association between hyperglycemia and duration of menopausal status after adjustment for age and other risk factors of diabetes with $p < .001$ & OR 1.04. But no association was found between neither age at menopause nor reproductive life span and the development of diabetes with p value 0.56, 0.92 respectively. There was a significant association between waist circumference and risk of developing diabetes in postmenopausal women with p value .009 & OR .001. No significant association between hysterectomy and risk of type 2 diabetes with p value 1. There was no significant association between HRT & diabetes with p value .6. However, there was a significant association between OCP and the risk of diabetes with p value .02. There was a significant association between gravidity and risk of diabetes with p .002 but not with parity with p value .16.

Conclusion: There was association between the duration of menopause and development of type 2 diabetes. Waist circumference representing central adipose tissue playing the major role in risk of diabetes in postmenopausal women.

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Introduction:-

Menopause signals the end of women's reproductive life. It has an important role in future disease risk. For example, an early age at menopause is associated with an increased risk of cardiovascular disease (CVD) and bone fractures (van, et al., 2003 & van, et al., 2004, Atsma, et al., 2006). However, an early menopause protects against breast, endometrial and ovarian cancer (Monnikhof, 1999, Dossus, et al., 2010 & Tsilidis, et al. 2011). Loss of ovarian function and subsequent decline in endogenous estrogens play as mediators of these differences in risk (Kelsey, et al., 1993). While the relationship between menopausal age and CVD risk is well established, its

association with type 2 diabetes, remains unclear, as the few epidemiological studies that have investigated this association yielded conflicting results (Di Donato, et al., 2005 & Luborsky, et al., 2003). However, this association can be explained by several evidences. First, menopause is associated with cessation of ovarian production of estrogen (Sowers, et al., 2003). This decline can be considered as one of the factors that play a pivotal role in development and progression of the metabolic syndrome (Salpeter, et al., 2006). This can be observed in postmenopausal women who received estrogen therapy and had a reduction in their fasting plasma glucose (FPG) levels (Kanaya, et al., 2003). Second, menopausal transition characterized by changes in the distribution of body fat with increasing in abdominal fat deposition under the effect of low estrogen and high androgen (Poehlman, et al., 1995). This is associated with a disturbance in the production of several hormones as adiponectin, leptin, ghrelin that are associated with insulin resistance and the metabolic syndrome (Lee, et al., 2009). Third, menopause is associated with continuation of androgen & testosterone production, that are associated with glucose intolerance in both premenopausal and postmenopausal women (Ding, et al., 2006). This could be observed in polycystic ovary syndrome (PCOS) which characterized by higher androgen levels, and greater risk of diabetes (Salley, et al., 2007).

Material and Methods:-

Subjects:-

Women were considered post menopause when they reported not having had any menses over the past twelve months or when they reported bilateral oophorectomy. They were considered in early menopause if they reported the former before the age of forty.

Case ascertainment and Verification:-

Diagnosis of diabetes were done according to ADA criteria (FBG \geq 126 mg/dl or PPG \geq 200 mg/dl or random blood glucose \geq 200 mg/dl plus symptoms or HA1C $>$ 6.5) (ADA, 2015).

Study design:-

All patients were subjected to complete history taking with stress on time of development of diabetes, duration of diabetes, history of hypertension, complication of diabetes including micro vascular (retinopathy, nephropathy & neuropathy), macro vascular (IHD, stroke) and diabetic foot, family history of diabetes, smoking, age at menarche, age at menopause, current and past medication including hormonal contraceptive drugs and hormonal replacement therapy, history of hysterectomy and/or oophorectomy and full obstetric history. A thorough clinical examination were performed to every subject with stress on blood pressure, anthropometric measures (height, weight, body mass index, waist circumference), and complication of diabetes. The following investigations were done to every subject including fasting and two hours post prandial plasma glucose, HbA1C, lipogram (total cholesterol, LDL-c, HDL-c and triglycerides), creatinine clearance, urinalysis for albuminuria. This was across sectional study on 400 post menopausal women who were divided into two groups: Group I : it included 155 diabetic patient. Group 2 : it included 254 non diabetic women. Then we divided group 1 into two sub groups, Group Ia: it included 43 diabetic patient before menopause. Group Ib: it included 112 diabetic patient after menopause

Statistical Analysis:-

The collected data were summarized in terms of mean \pm Standard Deviation (SD) and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the Chi-square test (χ^2) and Fisher's Exact Test (FET) to compare proportions as appropriate. The Student's t-test (t) was used to compare two means for normally distributed data, while the Mann-Whitney test (z) was used to compare non-normal data. The Analysis of Variance (ANOVA) test (F) was used to compare more than two means of normally distributed data and the Kruskal Wallis test (χ^2) was used to compare non-normal data. Pearson correlation coefficient (R) and Spearman correlation coefficient (rho; ρ) were used to examine the correlations between normally distributed data and non-normal data respectively. Stepwise logistic regression of being a case of diabetes conditioned on age, age of menopause, duration of menopause, reproductive life span, family history of diabetes, hormonal contraceptive drugs, hormonal replacement therapy, hysterectomy, parity, gravidity, BMI and waist circumference was carried out after the exclusion of colinear factors (age of menarche) to detect important predictors for diabetes in menopausal women. The corresponding P-values were obtained. A P-value $<$ 0.05 was considered statistically significant (S), a P-value $<$ 0.001 was considered statistically highly significant (HS), while a P-value $>$ 0.05 was considered statistically non-significant. The statistical analysis was conducted using STATA version 11 (STATA corporation, College Station, Texas).

Results:-

We found that age at menopause range was (31-63) with mean average (47.73 ± 5.02). The prevalence of diabetes in post menopausal women was 38%. There was a significant association between hyperglycemia and duration of menopausal status after adjustment for age and other risk factors for diabetes, the range of duration of menopause in diabetic women was (1-47) mean average (16.38 ± 9.09) and in non diabetic was (1-40) mean average (10.25 ± 9.29) with $p < .001$ & OR 1.04 . But no association was found between age at menopause and the development of diabetes as the range of age at menopause in diabetic women was (34-60) mean average (47.05 ± 5.29) and in non diabetic was (31-63) mean average (47.84 ± 4.99) with p value 0.56 . There was also no association between reproductive life span and development of diabetes as the range of reproductive life span in diabetic was (20-47) mean average (33.83 ± 5.6) and in non diabetic was (16-51) mean average (34.23 ± 5.62) with p value 0.92. There was a significant association between waist circumference (WC) and risk of developing diabetes in post menopausal women as the range of WC in diabetics was (65-165) mean average (115.66 ± 23.74) and in non diabetics was (57-170) mean average (109.23 ± 20.56) with p value .009 & OR .001. Our study showed no significant association between hysterectomy and risk of type 2 diabetes with p value 1 . we could not asses the association between oophorectomy and the risk of diabetes as there was recall bias . There was no significant association between HRT & diabetes with p value .6 , however , there was a significant association between OCP and the risk of diabetes with p value .02 . There was significant association between gravidity and risk of diabetes with p .002 but not with parity with p value 0.16.

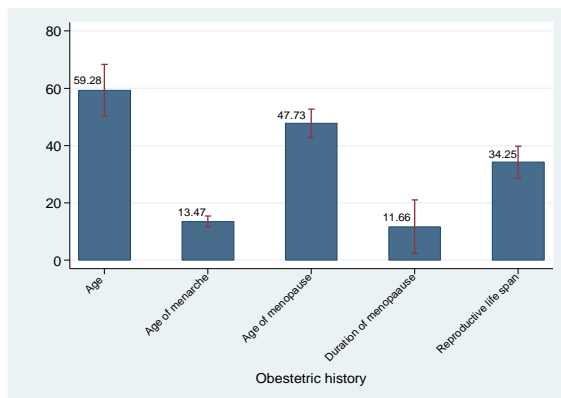


Fig. (1): Mean \pm SD & (range) of obstetric history including (age, age of menarche, age of menopause, duration of menopause, reproductive life span) in the study group.

Table (1): Reproductive factors of the study group

| Variable (No.=400) | | | |
|-----------------------------------|---------------------|-----|-------|
| Age (years) | 59.28±9.01; (40-87) | | |
| Age of menarche (years) | 13.47±1.87; (9-20) | | |
| Age of menopause (years) | 47.73±5.02; (31-63) | | |
| | <40- | 18 | 4.5 |
| | 40- | 62 | 15.5 |
| | 45- | 152 | 38.0 |
| | 50- | 130 | 32.5 |
| 55-63 | 38 | 9.5 | |
| Duration of menopause (years) | 11.66±9.37; (1-47) | | |
| Reproductive life span (years) | 34.25±5.49; (16-51) | | |
| Hormonal contraceptive drugs(OCP) | Yes | 131 | 32.75 |
| | No | 269 | 67.25 |
| Hormonal replacement therapy(HRT) | Yes | 5 | 1.25 |
| | No | 395 | 98.75 |
| Hysterectomy | Yes | 14 | 3.5 |
| | No | 386 | 96.5 |
| Oophorectomy | Yes | 5 | 1.25 |
| | No | 395 | 98.75 |
| Parity | 0.87±1.19;(0-7) | | |
| Gravidity | 4.41±2.07;(0-16) | | |

This table showed the reproductive factors of the study group: we can notice that age of these women range from 40 to 87 with (59.28 ±9.01), age of menarche was from 9-20 with (13.47±1.87), age of menopause range from 31-63 with (47.73±5.02), Duration of menopause also has a wide range from 1-47 with (11.66±9.37), reproductive life span range from 16-51 years with (34.25±5.49), 131 women had taken OCP while only 5 women received HRT, 14 women had underwent hysterectomy, gravidity ranges from 0-16 with (4.41±2.07), parity ranges from 0-7 with (0.87±1.19).

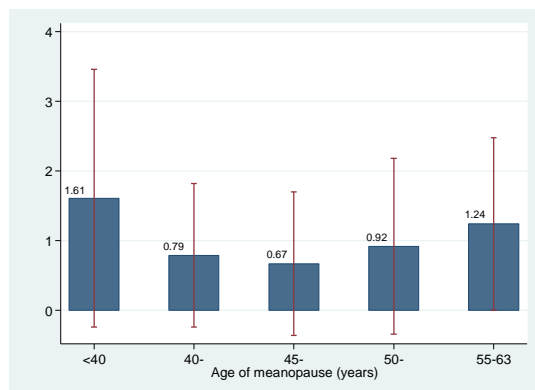


Fig. (2): Mean ±SD (range) of parity according to age of menopause, showing significant difference compared to <40 age group, with parity increasing more in this group compared to the rest.

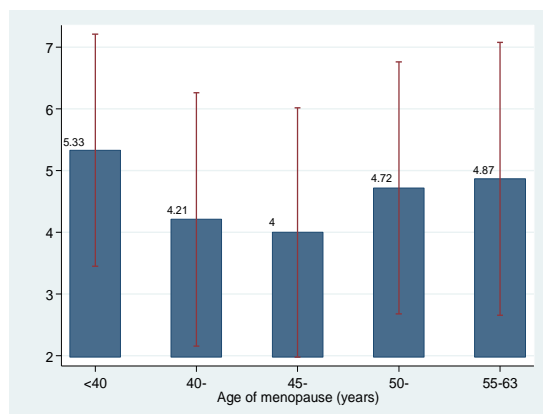


Fig.(3): Mean \pm SD; (range) of gravidity according to age of menopause, showing significant difference compared to <40 age group, with gravidity increasing more in this group compared to the rest.

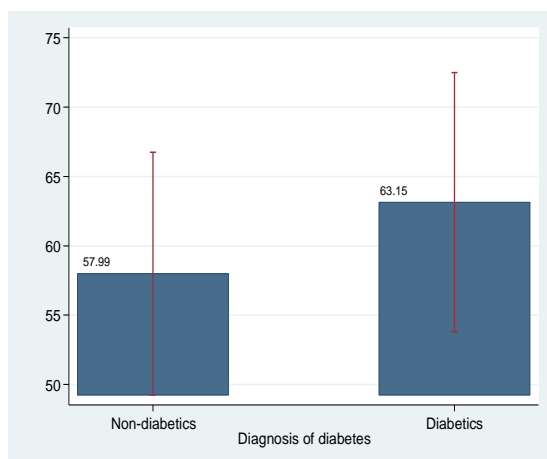


Fig.(4): Mean \pm SD of age between post-menopausal diabetic women 63.15 ± 9.33 , range from 44-88 and postmenopausal non diabetic women 57.99 ± 8.75 , range from 40-87 showing significant difference between both groups with p value < 0.001 .

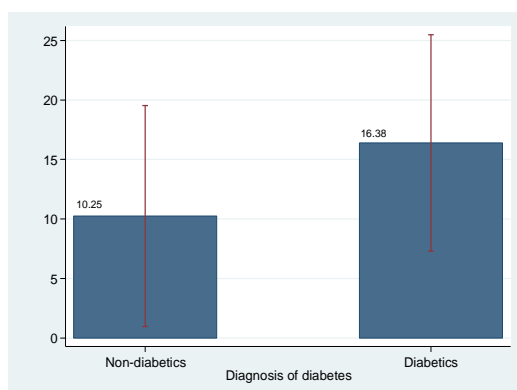


Fig. (5): Mean \pm SD of duration of menopause between diabetic women after menopause 16.38 ± 9.09 ; range 1-47 and non diabetic 10.25 ± 9.29 ; range 1-40 showing significant difference between both groups with p value < 0.001 .

Table (2): stratification of reproductive factors of the study group according to age of menopausal.

| Variable (No.=400) | | Age of menopause (years) | | | | | | | | | | Test | P |
|-------------------------------------|-------------------------|--------------------------|----------------|-------------------------|----------------|---------------------------|----------------|---------------------------|----------------|-----------------------------|----------------|---------------------|--------------------|
| | | <40 (No.=18) | | 40- (No.=62) | | 45- (No.=152) | | 50- (No.=130) | | 55-63 (No.=38) | | | |
| | | No. | % | No. | % | No. | % | No. | % | No. | % | | |
| Age (years) | Mean ±SD; (range) | 60.61±11.61; (40-82) | | 54.76±9.98; (42-80) | | 57.49±8.71; (47-85) | | 61.55±7.56; (52-87)†‡ | | 65.45±5.85; (57-80)†‡ | | F= 13.52 | <0.00 1 (HS) |
| Age of menarche (years) | Mean ±SD; (range) | 13.55±1.54; (11-16) | | 13.97±1.89; (9-17) | | 13.47±1.63; (10-18) | | 13.29±1.97; (9-19) | | 13.26±2.39; (10-20) | | F= 1.53 | 0.19 |
| Duration of menopause (years) | Mean ±SD; (range) | 24.55±11.99; (4-47) | | 12.74±10.91; (1-40)! | | 10.91±8.98; (1-39)! | | 10.45±7.87; (1-37)! | | 10.89±7.01; (2-30)! | | F= 10.47 | <0.00 1 (HS) |
| Reproductive life span (years) | Mean ±SD; (range) | 22.11±2.49; (16-25) | | 27.89±2.25; (24-34)! | | 33.1±2.13; (28-37)! †‡ | | 37.78±2.5; (31-44)! †‡ | | 42.92±2.86; (35-51)! †‡§ | | F= 440.41 | 0.001 (S) |
| Hormonal contraceptive drugs | Yes No | 8 10 | 44.44 55.56 | 25 37 | 40.32 59.68 | 55 97 | 36.18 63.82 | 36 94 | 27.69 72.31 | 7 31 | 18.42 81.58 | $\chi^2 =$ 8.60 | 0.07 |
| Hormonal replacement therapy | Yes No | 0 18 | 0.0 100.0 | 0 62 | 0.0 100.0 | 1 15 | 0.66 99.34 | 3 12 | 2.31 97.69 | 1 37 | 2.63 97.37 | FET | 0.47 |
| Hysterectomy | Yes No | 2 16 | 11.11 88.89 | 2 60 | 3.23 96.77 | 4 14 | 2.63 97.37 | 4 12 | 3.08 96.92 | 2 36 | 5.26 94.74 | FET | 0.33 |
| Oophorectomy | Yes No | 1 17 | 5.56 94.44 | 1 61 | 1.61 98.39 | 1 15 | 0.66 99.34 | 1 12 | 0.77 99.23 | 1 37 | 2.63 97.37 | FET | 0.21 |
| Parity | Mean ±SD; (range) | 1.61±1.85; (0- 7) | | 0.79±1.03; (0-4)! | | 0.67±1.03; (0-6)! | | 0.92±1.26; (0-6) | | 1.24±1.24; (0-4)†‡§ | | $\chi^2 =$ 10.88 | 0.03 (S) |
| Gravidity | Mean ±SD; (range) | 5.33±1.88; (2- 9) | | 4.21±2.05; (0-14)! | | 4±2.02; (0- 16)! | | 4.72±2.04; (0-12)†‡ | | 4.87±2.21; (0-9)†‡ | | $\chi^2 =$ 19.96 | <0.00 1 (HS) |

This table showed that the reproductive factors of the study group after dividing them into categories according to age of menopause in this table we can notice !Significant differences compared to <40 group; †significant differences compared to 40- group; ‡ significant differences compared to 45- group ; § significant differences compared to 45- group. It showed that menopausal women before 40y.o have significant difference in age with p value <0.001, duration of menopause p value <0.001 , reproductive life span p value 0.001 ,parity p value .03 and gravidity with p value <0.001.there was no significant association between age of menarche with p value 0.19, oophorectomy with p value 0.21,OCP s with p value 0.07,HRT with p value 0.47, hysterectomy with p value 0.33.

Table (3): Comparisons between postmenopausal diabetics and non-diabetics regarding reproductive factors.

| Variable (No.=400) | postmenopausal diabetics (No.=112) | | | postmenopausal non-diabetics (No.=245) | | | Test | P |
|--------------------------------|------------------------------------|-----|--------|--|--------|-----------------|----------|-------------|
| Age (years) | 63.15±9.33; (44-85) | | | 57.99±8.75; (40-87) | | | t= 5.06 | <0.001 (HS) |
| Age of menarche (years) | 13.22±1.85; (9-20) | | | 13.61±1.84; (10-19) | | | t= 1.85 | 0.06 |
| Age of menopause (years) | 47.05±5.29; (34-60) | | | 47.84±4.99; (31-63) | | | t= 1.36 | 0.17 |
| | <40- | 7 | 6.25% | 10 | 4.08 | $\chi^2 = 1.86$ | | |
| | 40- | 19 | 16.96% | 38 | 15.51 | | | |
| | 45- | 38 | 33.93% | 99 | 40.41 | | | |
| | 50- | 36 | 32.14 | 74 | 30.2 | | | |
| | 55-63 | 12 | 10.71 | 24 | 9.8 | | | |
| Duration of menopause (years) | 16.38±9.09; (1-47) | | | 10.25±9.29; (1-40) | | | t= 5.83 | <0.001 (HS) |
| Reproductive life span (years) | 33.83±5.6; (20-47) | | | 34.23±5.62; (16-51) | | | t= 0.63 | 0.53 |
| Hormonal contraceptive drugs | Yes | 26 | 23.21% | 89 | 36.33% | $\chi^2 = 6.05$ | 0.01 (S) | |
| | No | 86 | 76.79% | 156 | 63.67% | | | |
| Hormonal replacement therapy | Yes | 2 | 1.79% | 3 | 1.22% | FET | 0.65 | |
| | No | 110 | 98.21% | 242 | 98.78% | | | |
| Hysterectomy | Yes | 3 | 2.68% | 7 | 2.86% | FET | 1.00 | |
| | No | 109 | 97.32% | 238 | 97.14% | | | |
| Parity | 1.12±1.56; (0-7) | | | 0.73±0.93; (0-5) | | | z= 1.40 | 0.16 |
| Gravidity | 5.03±2.38; (0-16) | | | 4.21±1.89; (0-12) | | | z= 3.03 | 0.002 (S) |

This table showed that there was significant difference between the groups regarding age p value <.001, duration of menopause with p value <.001, OCP with p value .01 and gravidity with p value .002. there was no significant difference between the groups regarding age of menopause P value .17, reproductive life span p value 0.53, hormonal replacement therapy p value 0.65 Hysterectomy p value 1.00. Parity p value 0.16

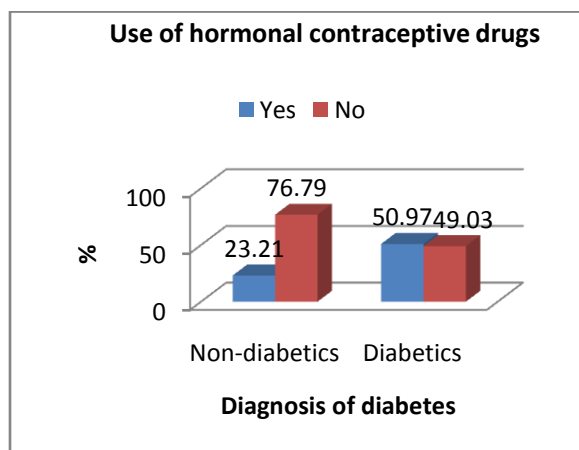


Fig.(6): Comparison between prevalence of usage of hormonal contraceptive drugs in post menopausal diabetic 36.33% and post menopausal non diabetics 63.67%, showing significant difference between both groups with p value 0.01

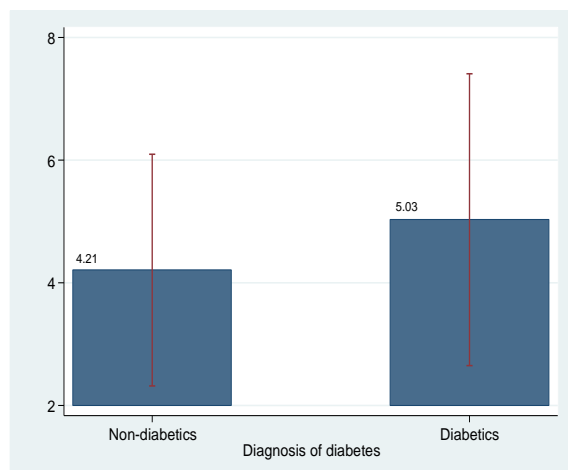


Fig. (7): Mean \pm SD of gravidity between postmenopausal diabetic women 5.03 ± 2.38 range from 0-16 and postmenopausal non diabetic 4.21 ± 1.89 range from 0-12 showing significant difference between both groups with p value 0.002

Table (4): Comparisons between postmenopausal diabetics and non-diabetics regarding clinical characteristics

| Variable (No.=400) | postmenopausal diabetics (No.=112) | | | Postmenopausal non-diabetics (No.=245) | | Test | P |
|--|------------------------------------|----|--------|--|--------|------------------|-------------|
| Hypertension | Yes | 67 | 59.82% | 64 | 26.12% | $\chi^2 = 37.57$ | <0.001 (HS) |
| | No | 45 | 40.18% | 181 | 73.88% | | |
| Duration of hypertension (years) (No.=131) | 9.61 \pm 7.44; (0.08-30) | | | 11.82 \pm 7.91; (1-40) | | t= 1.65 | 0.10 |
| SBP (mm Hg) | 130.98 \pm 14.52; (80-150) | | | 121.39 \pm 11.65; (100-160) | | t= 6.67 | <0.001 (HS) |
| DBP (mm Hg) | 83.03 \pm 11.61; (50-110) | | | 76.49 \pm 8.77; (50-110) | | z= 7.09 | <0.001 (HS) |
| Family history of diabetes | Yes | 51 | 45.54% | 36 | 14.69% | $\chi^2 = 6.14$ | <0.001 (HS) |
| | No | 61 | 54.46% | 209 | 85.31% | | |
| BMI (kg/m ²) | 33.47 \pm 7.44; (21-60) | | | 32.64 \pm 6.57; (16-51) | | t= 1.05 | 0.29 |
| Waist circumference (cm) | 115.66 \pm 23.74; (65-165) | | | 109.23 \pm 20.56; (57-170) | | t= 2.61 | 0.009 (S) |

This table showed that there was significant difference between the 2 groups regarding hypertension with p value <.001, SBP p value <.001, DBP p value <.001, Family history with p value <.001 and WC with p value .009. There was no significant difference between both groups regarding duration of hypertension with p value 0.10 & BMI with p value .29

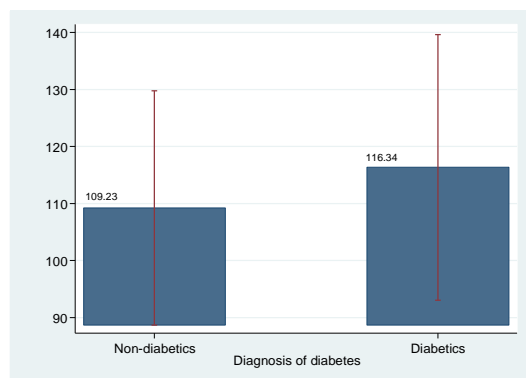


Fig. (8) : Mean \pm SD of WC between postmenopausal diabetic women 115.66 ± 23.74 ; range from 65-165 and postmenopausal non diabetic 109.23 ± 20.56 ; range from 57-170 showing significant difference between both group with p value .009.

Table (5): Multiple logistic regression analysis

| Variable | OR | 95% CI | P |
|--|------|-------------|-------------|
| Family history of diabetes Yes vs. no | 5.42 | 3.33 - 8.81 | <0.001 (HS) |
| Duration of menopause (years) | 1.04 | 1.02 - 1.07 | 0.001 (S) |
| Waist circumference (cm) | 1.01 | 1.00 - 1.02 | 0.04 (S) |

There was increased risk of diabetes in menopausal women with positive family history of diabetes compared to those without family history (OR; 95% CI: 5.42; 3.33-8.81). Also, the risk of diabetes was increased by the increased duration of menopause (OR; 95% CI: 1.04; 1.02-1.07) and waist circumference (OR; 95% CI: 1.01; 1.00-1.02).

Discussion:-

Menopause is the eventual end of every women's reproductive life, which has specific hormonal and metabolic profiles that differ from that of women in the child bearing period (Burger,1994). These hormonal changes are associated with an increased risk of cardiovascular disease (CVD) and bone fractures (van,et al,2003, van,et al,2004 & Atsma,et al, 2006). However, these hormonal changes protect against breast, endometrial and ovarian cancer (Monninkhof, 1999, Dossus, et al., 2010 & Tsilidis, et al., 2011). Diabetes as one of the major risk factors for CVD, had been noticed to be more common in post menopausal women (Yang,et al,2010). However, the studies regarding the relationship between menopausal age and diabetes were conflicting with either an or no association (Luborsky, et al, 2003 & Di Donato, et al, 2005). Our study showed that age at menopause ranged from 31 to 63 years (47.73 ± 5.02). This result was consistent with a study which reported that age of menopause was approximately between 40 and 60 years with a mean of 51 years (Kok,et al.,2005). However, other studies reported mixed results regarding menopausal age (Malacara, et al.,1997). We found that the prevalence of diabetes in post menopausal women was 38%. There was a significant association between hyperglycemia and duration of menopausal status in our study after adjustment for age and other risk factors for diabetes with p value < .001 and OR .001. But a significant correlation between duration of menopause and age of those women was noticed with p value < .001. Our results were consistent with data from study which found that the high prevalence of dysglycemia was associated with older age and a postmenopausal state independently and additively, menopause was associated with the presence of dysglycemia even among women aged less than 50 years at the time of examination (Yoriko

,et al.,2013). Other studies had shown a higher percentage of metabolic syndrome in post menopausal groups (Tandon & Ruan, et al.,2010). On the other hand, in women at high risk for diabetes who participated in the Diabetes Prevention Program (DPP), no association was found between neither natural menopause nor bilateral oophorectomy and increased risk of developing diabetes after adjustment for age (Kim,et al., 2011). These conflicting results regarding relation between menopause and diabetes may be due to: first, the definition of the diagnosis of diabetes differed among these studies. Second, assessment of the menopausal state usually was based on self-reported responses. Third, some differences existed in age at menopause onset. Fourth, these studies did not measure the associations between menopause and the key mediators of glucose tolerance, specifically insulin secretion, insulin resistance and other biomarkers. Our study showed that high waist circumference was considered as a risk factor for development of DM in postmenopausal women. This could be inferred from the following: we found a significant relation between waist circumference (WC) and risk of developing diabetes in post-menopausal women with p value .001, and OR 1.01. This was consistent with a study which found that menopausal transition characterized by an increased body fat mass and central adiposity, and decreased lean body mass resulting in increase in cardio metabolic risk factors (Szmulowicz,et al., 2009 & Shruti,et al., 2012). However, some studies explained that menopause is a phenomenon of aging in women (Mazariegos, et al., 1884 & Baumgartner, et al., 1993) they stated that aging is associated with physical inactivity, decrease in energy metabolism and increase in food intake that lead to weight gain, higher waist diameters and waist-to-hip ratios in older women. In our study we found that family history of diabetes was an independent risk factor of diabetes, it was more important than duration of menopause and waist circumference with p value < 0.001 and OR 5.42. This was consistent with study that found people without a family history of diabetes versus those who have a family history of diabetes are two to six times as likely to have type 2 diabetes (Harisson,2003). Our study showed that neither the age of menopause nor the reproductive life span had a significant impact on the development of diabetes with p value .7 and .5 respectively. This can be explained by the fact that age of menarche was subjective and self-reported so, there was a significant recall bias regarding the age of menarche and consequently the reproductive life span. Our results were consistent with several studies (Mishra, et al., 2007 & Janssen, et al., 2008). However, In the prospective case-cohort study (EPIC-Inter Act study) (Brand,et al.,2013) they found that an earlier age at menopause and a shorter reproductive life span was associated with a greater risk of type 2 diabetes. The hazard of type 2 diabetes was 32% higher in women who entered their menopause before 40 years of age compared with women having their menopause at 50–54 years. Also, in the NHEFS (National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study) (Duke, et al.,2014) they found that an earlier age at menopause and a shorter reproductive life span also exhibited a linear relationship with the development of diabetes irrespective of type of menopause (P for trend = 0.001). The reproductive life span represent the child bearing period and so it may be associated with development of diabetes due to repeated pregnancies and deliveries this can be confirmed in our study in which we noticed that multi gravidity had a significant association with diabetes with p value .002 than multiparty with p value .16. This result was consistent with several studies that suggested that gravidity and parity, particularly five or more live births, might be associated with diabetes (Kritz,et al., 1989 & Hanley,et al., 2002). Our study showed no significant association between hysterectomy and risk of type 2 diabetes with p value 1. But as regarding oophorectomy we cannot assess this relation as there was recall bias. This was consistent with a large Italian study among women entering menopause clinics, as they did not find a significant association in women with surgical menopause and diabetes (Di Donato,et al., 2005). On the other hand, In the NHEFS (Duke, et al.,2014) they found that hysterectomy concomitant with BSO was associated with incident diabetes mellitus independent of confounding factors as women grow older. This controversy regarding relation between surgical menopause and diabetes can be explained by: First, the definition of surgical menopause was inconsistent. Second, associations between menopausal age and risk of chronic diseases are usually attributed to a short or prolonged exposure to endogenous estrogens. In contrast to breast cancer, where the available evidence on reproductive factors, endogenous estrogen levels, and exogenous estrogen supplementation all points to an important role of estrogen exposure (Persson,2000). Third, recall bias of time and type of operation. Our study showed that HRT had a significant protective role against development of diabetes with p value .6. However, the risk of diabetes increased substantially in women who were receiving OCP with p value .05. A trial on 199 women without diabetes showed that HRT decreased fasting insulin and HbA1c in women without diabetes (Davidson,et al., 2000). However, a large trial of unopposed estrogen in women who had a hysterectomy reported a non significant reduced risk of diabetes based on fasting glucose. Although approximately 40% of that cohort had undergone bilateral oophorectomy, results were not reported separately by oophorectomy history (Bonds,et al.,2006). In the (PEPI) study, 875 women treated for 3 years with CEE plus various (MPA) medroxy progesterone acetate regimens had a 2–3% decrease in fasting but a 2–7% increase in 2-h glucose, without significant change in fasting or 2-h insulin or in weight or abdominal girth (Espeland,et al., 1998). However, the (HERS) that was on 2,763 women with CHD,

27% of whom had diabetes, who were treated for 4.1 years with CEE plus MPA or placebo, revealed that fasting glucose showed a greater increase in the placebo group, with a 35% decrease in risk of development of diabetes (based only on fasting glucose measurement) among 1,811 normal women and 218 with impaired fasting glucose (Vittinghoff, et al., 2003). Experimental data support a protective role for estrogens in glucose metabolism. In rodents, ovariectomy (loss of oestrogen) increases food intake and body fat mass, and these effects are reversed by oestrogen therapy. Mice rendered estrogen deficient by a targeted mutation in the aromatase gene, which is required for estrogen production, are obese and insulin resistant. Similarly, the rare event of a mutation in the aromatase gene in human, and hence inability to make oestrogen, resulted in insulin resistance, type 2 diabetes, fatty liver and atherosclerosis (Maffei, et al., 2004). However, It was reported that estrone but not estradiol levels were associated with increased risk of incident T2DM in a cohort of community-dwelling men. (Guneet, et al., 2013). Apart from the dramatic reduction in endogenous estrogen, other menopause-related factors may play a role in explaining the observed increase in diabetes risk with early menopause. The menopausal transition is characterized by a shift toward androgen predominance & a decrease in sex hormone-binding globulin levels (Rannevik, et al., 1995). These hormonal changes has been linked to a higher risk of type 2 diabetes in postmenopausal women (Ding, et al., 2007). In a study ,on PCOs women, they found higher frequency of metabolic syndrome and increased carotid artery intima-media thickness in early adulthood in PCOS patients, this can be explained as metabolic syndrome and PCOS were linked to insulin resistance at the cellular level, suggesting different degrees of genetic and functional defects (Kohen, et al., 2003). In our study we also assessed the risk factors that may lead to early menopause and we found that it is mainly associated with increasing the number of parity with p value .03 and gravidity with p value <.001 and with high total cholesterol with pvalue.02. However, neither diabetes nor hypertension could not be considered as risk factors of early menopause. The cross sectional study included 6079 women aged 40-59 years from 11 countries in Latin America ,showed that the risk of being postmenopausal in women aged 40-44 years after adjustment for confounding factors, was almost three times as high in those with diabetes than in those without diabetes (odds ratio 2.76 (95% confidence interval 1.32 to 5.67)). But this increased risk of early menopause with diabetes disappeared in women older than 50 year old (Monterrosa, et al., 2013). The FAD Study follow-up is now underway and provides a unique opportunity to prospectively evaluate the menopause transition among type 1 diabetic women. To our knowledge, such an investigation has never been conducted and will reveal critical information about premature aging, autoimmunity, and early menopause among women with type 1 diabetes (Dorman, et al., 2001).

Limitations Of Our Study:-

1. Because the assessment of menopausal and menarche status was based on self-report, there is the possibility of misclassification of menopausal status among the women studied.
2. we can't asses role of bilateral oophorectomy on diabetes , also we didn't have enough cases of PCO to asses it as a risk for diabetes.
3. we didn't asses visceral adipose tissue by neither CT nor MRI which are more accurate than simple measuring of the waist circumference.
4. we cannot rule out the possibility that residual confounding influenced the results.

Conclusions:-

There is relation between the duration of menopause and development of diabetes type 2 .Waist circumference representing central adipose tissue plays a major role in diabetes risk in postmenopausal women. There is no relation between neither age at menopause nor reproductive life span and diabetes. Gravidity not parity increases the risk of diabetes. There is a protective role of HRT against diabetes , however , there is risk of diabetes with women who use OCP. There is no significant association between hysterectomy and risk of type 2 diabetes. Early age at menopause is mainly associated with increasing the number of parity with and gravidity , high total cholesterol. However, neither diabetes nor hypertension could not be considered as risk factors of early menopause.

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