Lipid Profiling And Estrogen Levels Of Pre-Menopausal And Post-Menopausal Diabetic Women In Port Harcourt

Ikimi, Tarila, Ben-Chioma, Adline Erima and Brown, Holy

Department of Medical Laboratory Sciences, Rivers State University, Npkolu, Port Harcourt, Nigeria.

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ABSTRACT

Cardiovascular risk factors in women are not properly investigated nor treated and events are frequently lethal. Both menopause and type 2 diabetes substantially increase cardiovascular risk in the female sex, promoting modifications on lipid metabolism and circulating lipoproteins. Pregnancy and delivery are important events in the life of a woman. Gestation leads to a cascade of physiological change in sex hormones levels, haemodynamics, oxidative stress, and so on, which can exert complex influences on major organ systems, therefore, may also have long-term implications for women’s health. This study was aimed to ascertain the relationship between oestrogen levels and lipid profile of pre-menopausal and post-menopausal diabetic women resident in Port Harcourt Metropolis. This study included a total of one hundred and eighty study participants comprising of ninety menopausal and ninety premenopausal diabetic women assessing care at the Braithwaite Memorial Specialist Hospital. All subjects were female diabetics and were aged between 18 and 80 years. Out of the 90 menopausal diabetic subjects, 48 subjects were obese while 42 subjects were non-obese. Thirty-three (33) subjects had parity of 1-2, thirty-two (32) had parity of 3 while 25 had parity between 4 and 5. Glucose levels and lipid profile were estimated using spectrophotometric method, while estrogen levels were estimated using Enzyme Linked Immunosorbent Assay (ELISA). The results show that there was significantly higher (p=0.000) Estradiol levels for menopausal women compared with those of pre-menopausal women. The mean values and standard deviations of TG, TC, HDL, LDL and LDL/HDL ratio for pre-menopausal women were observed to be 1.02±0.38mmol/L, 3.92±0.71mmol/L, 1.56±0.59mmol/L, 2.18±0.71mmol/L and 2.58±1.12 respectively. Whilst, 1.10±0.49mmol/L, 3.79±0.80mmol/L, 1.17±0.45mmol/L, 2.31±0.77mmol/L and 2.35±1.59 were respectively observed for menopausal women. There were significantly lower HDL (p=0.001) and LDL/HDL (p=0.01) between both groups. There were no significant differences between other parameters. The study has shown that there is increased cardiovascular morbidity and mortality in menopausal diabetic women as compared to pre-menopausal diabetic women which is evidenced in the reduction in the levels of estradiol in the former. The study has also shown that multiparous diabetic women are more likely to have cardio protective properties than diabetic women with lower parity.
INTRODUCTION:
Pre-menopause is period occurs 3-10 years before a woman enters menopause, when the ovaries start reducing the amount of estrogen they produce, [1]. While Menopause is that point in a woman’s life when permanent cessation of menstruation occurs following the loss of ovarian activity [2]. Much focus has been on explaining the increased risk of cardiovascular disease in post-menopausal women and on estrogen-induced effects producing a more beneficial lipid profile in the pre-menopausal women. The 25-50% of the cardiovascular benefit seen in pre-menopausal women arising from changes in lipid profiles has been known to reduce once one is diabetic [3].

There is increasing evidence from epidemiological studies that females at older age were prone to Type 2 Diabetes Mellitus (T2DM) than male. Moreover, post-menopausal diabetic females have been implicated to have higher elevated risk of cardiovascular disease. However, it is still uncertain whether the estrogen itself contributes significantly to this increase in risk [4]. It has been shown that post-menopausal women have less cardiovascular lipid profile levels [5]. However; pre-menopausal women are not completely free. No significant difference in the triglycerides between the diabetic premenopausal and postmenopausal females, a significant reduction in the level of High Density Lipoprotein-cholesterol in the postmenopausal group and significant increase in the value of the total cholesterol of pre-menopausal subjects have been reported [6].

Understandably, the main focus of clinicians has been on how to tackle these problems and this invariably results to neglecting diabetes in female subjects. In this study, we ascertained the clinical utility of adopting estrogen and lipid levels as indicator amongst the study participants. Studies[7,8] have shown that there is a decline in oestrogen level in an apparently healthy woman as she approaches menopause. It was also reported [7] that some of the cardio-protective effect of oestrogen, particularly in the reduction of LDL-cholesterol level are lost in menopause. But it is not clear, as there is a dearth of information on the effect of the metabolic complications of diabetes on pre- and post-menopausal women. That is, as to whether it enhances, by whatever mechanism certain biochemical processes that increase/decrease oestrogen levels and lipid profile as the woman approaches menopause. Invariably, can diabetes change lipid profile levels during normal physiological transition from pre-to post menopause? Also, can diabetes affect lipid profile in different parities in women at pre-menopause? This study was aimed at ascertaining the relationship between oestrogen levels and lipid profile levels of pre-menopausal and post-menopausal diabetic women attending Braithwaite Memorial Specialist Hospital (BMSH), Port Harcourt, Nigeria.

The study subjects were women recruited from the Braithwaite Memorial specialist hospital, Port Harcourt, Nigeria. Subjects were known diabetics and only females of pre-menopausal and post-menopausal age were recruited.

MATERIALS AND METHODS
This study was a cross-sectional study. Samples were randomly collected at a point from 180 women within the ages of 38-75years.

Inclusion Criteria / Exclusion Criteria
The following subjects were recruited for the study: Premenopausal diabetic women - women who are few years (about 2-10 years) before menopause (i.e., 38 – 43 years), (Rachel, 2017). Post-menopausal diabetic women (aged between 48-75 years). Anyone living outside the sampled study area and less than 38 years of age was excluded. Diabetic subjects who were pregnant were also excluded.

Ethical Considerations
This study was cleared by the Ethics committee of Braithwaite Memorial Hospital. Written and Verbal informed consent was obtained from all
respondents and the study purpose was explained to them.

Acquisition of Socio-demographic Data and Biochemical Parameters
Questionnaire was administered to subjects that gave consent. The questionnaire covered demographic and health history information, including race/ethnicity, age, educational attainment, family history of DM, family history of metabolic disorders, depression, self-report of heart disease, use of contraceptives/hormone therapy use, and smoking/alcohol status and dates of cessation of menstrual cycle. Blood sample was collected for lipid profile (TCHOL, HDL, TG, LDL) fasting blood glucose, and estrogen determination.

Weight and Height
The subjects were weighed without their shoes using a bathroom scale. The height was measured using a meter rule. The blood pressure was done using automatic blood pressure monitor (sphygmomanometer).

Statistical Analysis
Data was entered and analyzed using statistical package for social sciences (SPSS) version 21 statistical software package. Frequencies/percentages and mean/SD was used for the descriptive analysis of the data. Chi-square, Pearson correlation and Analysis of Variance (ANOVA) were used to compare dependent and independent variables. Hypothesis tests were conducted to compare summary statistics at 95% significance level.

RESULTS
Comparison of Biophysical and Biochemical Parameters of Post-Menopausal and Pre-menopausal Women.
The details of comparison of biophysical and biochemical parameters of post-menopausal and pre-menopausal women are shown in Table 1. The mean age for post-menopausal women was 64.32 ± 5.46 years which was significantly higher (p=0.000) than that of premenopausal subjects 37.4 ± 4.31 years. Also, the Mean values and standard deviation for Body Mass Index of post-menopausal subjects was 26.34 ± 4.55kg/m², was significantly higher than the BMI of pre-menopausal subjects (23.41 ± 2.33) kg/m² (p=0.000). The table also showed the Mean and standard deviation for Fasting Blood Sugar of Post-menopausal subjects as 10.95 ± 5.25mmol/L, which showed no significant difference (p=0.725) from that of premenopausal subjects 10.69 ± 4.14mmol/L. Also shown are the Mean values and standard deviation values for Glycated Haemoglobin (HbA1c) (measured in percentage) for Menopausal subjects as 8.11±2.33% which was similar to that of pre-menopausal subjects 9.05±6.36% (p=0.1892). The table showed the Mean and standard deviation of Estradiol (measured in pg/ml) of Post-menopausal subjects as 21.53±14.93pg/ml. This was observed to be significantly higher (p=0.000) than that of premenopausal women 11.80±5.55pg/ml (p=0.0001)

Table 1 Comparison of Biophysical and Biochemical Parameters of Post-menopausal and Pre-menopausal Women.

<table>
<thead>
<tr>
<th></th>
<th>Post-menopausal (N= 90)</th>
<th>Premenopausal (N= 90)</th>
<th>p-values</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE yrs</td>
<td>64.32 ± 5.46</td>
<td>37.4± 4.31</td>
<td>0.00001</td>
<td>S</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>26.34 ± 4.55</td>
<td>23.41 ± 2.33</td>
<td>0.00001</td>
<td>S</td>
</tr>
<tr>
<td>FBS mmol/L</td>
<td>10.95 ± 5.25</td>
<td>10.69 ± 4.14</td>
<td>0.7245</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1C %</td>
<td>8.11 ± 2.33</td>
<td>9.05 ± 6.36</td>
<td>0.1892</td>
<td>NS</td>
</tr>
<tr>
<td>ESOL(pg/ml)</td>
<td>21.53 ± 14.93</td>
<td>11.80 ±5.55</td>
<td>0.0001</td>
<td>S</td>
</tr>
</tbody>
</table>

S – Significant NS - Not significant
Lipid Profile of Post-menopausal and Pre-menopausal Subjects

Table 2 showed the Mean and standard deviation and p values of lipid profile of both Post-menopausal and pre-menopausal women. Triglycerides, measured in mmol/L of post-menopausal subjects was 1.02±0.38mmol/L which was similar to that of premenopausal subjects 1.10±0.49mmol/L (p=0.180). The table also showed the Mean and standard deviation of Total Cholesterol of Post-menopausal subjects as 3.92±0.71mmol/L which was significantly lower than that of premenopausal subjects 3.79±0.80mmol/L (p=0.05). Mean and standard deviation of High Density Lipoprotein of Post-menopausal subjects was observed to be 1.56±0.59mmol/L, while that of premenopausal women was 1.17±0.45mmol/L. There was a significantly higher (p=0.000) values in Post-menopausal women compared with that of Pre-menopausal women. Shown in table 4.3 are also the mean values of LDL for both groups. The Mean and standard deviation of Low Density Lipoprotein of Post-menopausal subjects was 2.18±0.71mmol/L which was similar to that of premenopausal subjects 2.31±0.77mmol/L (p=0.245). The table also showed the mean LDL/HDL ratio for Post-menopausal (2.58 ± 1.12) and premenopausal (2.58 ± 1.12). A significantly lower (p=0.01) difference in mean was observed after comparing the mean values of both groups.

Table 2 Lipid profile of Post-menopausal and Pre-menopausal subjects

<table>
<thead>
<tr>
<th></th>
<th>Menopause</th>
<th>Pre-menopause</th>
<th>p-values</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 90</td>
<td>N= 90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG mmol/L</td>
<td>1.02 ± 0.38</td>
<td>1.10 ± 0.49</td>
<td>0.1804</td>
<td>NS</td>
</tr>
<tr>
<td>TC mmol/L</td>
<td>3.92 ± 0.71</td>
<td>3.79 ± 0.80</td>
<td>0.2423</td>
<td>NS</td>
</tr>
<tr>
<td>HDL mmol/L</td>
<td>1.56 ± 0.59</td>
<td>1.17 ± 0.45</td>
<td>0.0001</td>
<td>S</td>
</tr>
<tr>
<td>LDL mmol/L</td>
<td>2.18 ± 0.71</td>
<td>2.31 ± 0.77</td>
<td>0.2448</td>
<td>NS</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>2.58 ± 1.12</td>
<td>2.35 ± 1.59</td>
<td>0.01</td>
<td>S</td>
</tr>
</tbody>
</table>

S – Significant NS - Not significant

Comparison between post-Menopausal 3 Parity Subjects and Pre-menopausal Subjects

Table 3 showed comparison between post-menopausal diabetic women with 3 parity subjects and pre-menopausal diabetic subjects. From the table, the mean age values for post-menopausal 3 parity and pre-menopausal diabetic subjects were recorded as 62.68 ±5.36 and 37.4± 4.31 years respectively. Mean BMI values were respectively recorded as 27.22 ± 4.67 and 23.41 ± 2.33kg/m². The table also showed mean values for FBS, HbA1C, TG, TC, HDL, LDL, LDL/HDL ratio and Estradiol for post-menopausal 3 parity and pre-menopausal diabetic subjects. From the table, only the mean values for age (p=0.0001), BMI (p=0.0001), HDL (p=0.0002) and estradiol (p=0.003) were significantly lowered in pre-menopausal subjects. While mean value for HbA1c (p=0.04) was significantly higher in pre-menopausal subjects.
Table 3 Comparison Between 3 Parity Diabetic Subjects and Premenopausal Diabetic Subjects

<table>
<thead>
<tr>
<th></th>
<th>Age yrs</th>
<th>BMI kg/m²</th>
<th>FBS mmol/L</th>
<th>HbA1C %</th>
<th>TG mmol/L</th>
<th>TC mmol/L</th>
<th>HDL mmol/L</th>
<th>LDL mmol/L</th>
<th>LDL/HDL</th>
<th>ESOL(pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Parity (N=32)</td>
<td>62.68 ±</td>
<td>27.22 ±</td>
<td>10.42 ±</td>
<td>7.46 ±</td>
<td>0.99 ±</td>
<td>3.81 ±</td>
<td>1.55 ±</td>
<td>2.36 ±</td>
<td>2.67 ±</td>
<td>21.0 ± 15.97</td>
</tr>
<tr>
<td>Premenopausal (N=90)</td>
<td>37.4 ±</td>
<td>23.41 ±</td>
<td>10.69 ±</td>
<td>9.05 ±</td>
<td>1.10 ±</td>
<td>3.79 ±</td>
<td>1.17 ±</td>
<td>2.31 ±</td>
<td>2.35 ±</td>
<td>11.8 ± ± 5.55</td>
</tr>
</tbody>
</table>

P-Value          | 0.0001  | 0.0001    | 0.7928     | 0.0402  | 0.1777    | 0.8936    | 0.0002     | 0.5334     | 0.1297   | 0.003       |
Remark           | S       | S         | NS         | S       | NS        | NS        | S          | NS         | S        | S           |

Comparison Between Post-Menopausal 4-5 Parity Diabetic Subjects and Premenopausal Diabetic Subjects

Table 4 showed comparison between post-menopausal diabetic women with 4-5 parity subjects and pre-menopausal diabetic subjects. The table above showed that 4-5 Parity Diabetic Pre-menopausal subjects had mean values for Age was 65.44 ± 4.44 years, BMI 25.50 ± 4.84(kg/m²), FBS 10.86 ± 5.06 (mmol/L), HbA1C 8.4 ± 2.46%, TG 1.02 ± 0.38(mmol/L), TC 3.81 ± 0.64(mmol/L), HDL 1.47 ± 0.64(mmol/L), LDL 2.04 ± 0.81(mmol/L), LDL/HDL ratio 3.041 ± 1.32 and ESOL 23.71 ± 14.59(pg/ml). When these mean values where statistically compared with mean values for premenopausal women, age (p=0.0001), BMI (p=0.045), HbA1C (p=0.037), LDL/HDL ratio (p=0.024) and ESOL (p=0.0005) were significantly lowered. Mean LDL level was significantly higher (p=0.032), while the mean FBS, HbA1C, TG and TC were not significantly different.

Table 4 Comparison Between 4-5 Parity Diabetic Pre-menopausal Subjects and Premenopausal Diabetic Subjects

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>BMI (kg/m²)</th>
<th>FBS (mmol/L)</th>
<th>HbA1C (%)</th>
<th>TG (mmol/L)</th>
<th>TC (mmol/L)</th>
<th>HDL (mmol/L)</th>
<th>LDL (mmol/L)</th>
<th>LDL/HDL</th>
<th>ESOL(pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5 N=25</td>
<td>65.44 ± 4.44</td>
<td>25.50 ± 5.06</td>
<td>10.86 ±</td>
<td>8.4 ± 2.46</td>
<td>0.38 ±</td>
<td>0.64 ±</td>
<td>0.64 ±</td>
<td>0.81 ±</td>
<td>23.71 ±14.59</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>37.4 ± 23.41</td>
<td>10.69 ± 9.05±6.36</td>
<td>1.10 ±</td>
<td>3.79 ±</td>
<td>1.17 ±</td>
<td>2.31 ±</td>
<td>2.35 ±</td>
<td>11.80 ± 5.55</td>
<td></td>
</tr>
<tr>
<td>N=90</td>
<td>4.31 ± 2.33</td>
<td>4.14 ± 9.05±6.36</td>
<td>0.49 ±</td>
<td>0.80 ±</td>
<td>0.45 ±</td>
<td>0.77 ±</td>
<td>1.59 ±</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>P-Value</td>
<td>0.0001</td>
<td>0.0459</td>
<td>0.8789</td>
<td>0.4343</td>
<td>0.3744</td>
<td>0.992</td>
<td>0.037</td>
<td>0.0241</td>
<td>0.003</td>
</tr>
<tr>
<td>Remark</td>
<td>S</td>
<td>S</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
</tbody>
</table>
DISCUSSION
In this study a total of one hundred and eighty (180) participants comprising of ninety menopausal and ninety premenopausal diabetic women getting care at the Braithwaite Memorial Specialist Hospital were recruited for the study. All subjects were female diabetics, aged between 38 and 75 years. Out of the 90 menopausal diabetic subjects, 48 subjects were obese while 42 subjects were non-obese. Thirty-three (33) subjects had parity of 1-2, thirty-two (32) had parity of 3 while 25 had parity between 4 and 5. From the results of this study, Post-menopausal diabetic women had higher BMI when compared to pre-menopausal diabetic women. This may be due to the effect of estrogen in the latter. This is in line with [9] that reported that higher BMI were observed for Post-menopausal subjects giving reason that around the time of Post-menopausal, several changes occur which could contribute to increase in BMI as well as an increase in the risk of cardiac disease, this can be exacerbated in diabetes due to the link between diabetes and dyslipidemia.

This study also showed that the mean value of Estradiol for Post-menopausal diabetic subjects was significantly higher (p=0.000) than that of premenopausal women. This is in contrast to the trend in normal subjects. This is clear evidence that diabetic complications may have effect in the production/synthesis of estradiol. It had been reported that there was a two fold increase in CVD risk in post-menopausal women compared to pre-menopausal women [10]. However, in patients with diabetes, premenopausal women lose some protective factors observed in their healthy counterparts. A worsening of the plasma lipid profile may contribute to the loss of CVD protection seen in diabetic women [11,12]. Also, the pre-menopausal advantage in the clearance of dietary lipids in healthy subjects is not seen in premenopausal women with Type 2 Diabetes Mellitus [11]. This is in tandem with the findings of this study as there is a significantly lower estradiol level in premenopausal diabetic women. Furthermore, diabetes can attenuate protective effects of oestrogen in premenopausal status [13]. Based on that, it implies that the higher estradiol levels in post-menopausal women, as seen in this study, may not have any protective effect probably due to the effects posed by diabetic complications. Studies from [14,13], show that oestrogen deficiency appears to be associated with an increased risk of cardiovascular events. In non-diabetic women, one of the beneficial effects of oestrogen in terms of the prevention of CVD and its risk factors is the increase in the basal release of nitric oxide (NO) from endothelial cells, oestrogen has beneficial effect on the vascular endothelium and on cholesterol concentrations, [15,16]. The mean and standard deviation for Triglycerides showed that there was no significant difference (p=0.180) between both groups for triglyceride levels.

Hypercholesterolemia is the major driving cause for CVD in both men and women (as reported by [17], and its treatment has been associated with significant reductions in morbidity and mortality. [18] reported that post-menopausal subjects tend to metabolize lipid that becomes more atherogenic than their pre-menopausal counterpart. After menopause, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-c) usually increase, and these changes are accompanied by a decrease in high-density lipoprotein cholesterol (HDL-c) and an increase in triglycerides (TG) [19]. In addition to these major lipid abnormalities, also modifications in size and density of these lipoprotein particles are expected to happen after the loss of ovarian hormonal production. This partially explains the increased cardiovascular risk in postmenopausal women with diabetes, particularly among those with an earlier onset of menopause [20].

This study also showed that the Mean and standard deviation of Total Cholesterol of Post-Menopausal subjects were significantly lower than that of premenopausal women (p=0.05). However, [21] had reported a significantly higher total cholesterol levels in post-menopausal subjects compared to premenopausal (p=0.023) subjects. In this study, there was a significantly lower (p=0.000) mean HDL values of pre-menopausal subjects when compared with that of post-menopausal women. Low Density Lipoprotein cholesterol (LDL-c) for premenopausal and Menopausal subjects was statistically not significant (p=0.245). This is not in tandem with some studies. [22] observed an increase in LDL-c in premenopausal
diabetic women compared to menopausal and post-menopausal women. Although, aging itself is associated with an increase in LDL-c, in part due to a reduction in its catabolism by the liver. However, the higher levels of total cholesterol, LDL-c and apo-B found after menopause compared to premenopausal ones are not completely explained by aging [23]. Additionally, in the post-menopausal compared to premenopausal diabetic women, increased LDL-c concentration was maintained after adjustments for age and several confounders. Smaller denser Apo-B rich LDL particles are more frequent in postmenopausal women, while larger and buoyant LDL is decreased [22]. LDL/HDL ratio for menopausal and premenopausal was significantly lower (p=0.01) after comparing the mean values of both groups.

Studies that have shown an association between pregnancy and abnormal metabolic risk factors have largely been conducted on pregnant women or women of reproductive age, [24], and it is unclear whether any effect of repeated pregnancies on these risk factors persists into later life. Parity has been shown to be associated with coronary heart disease (CHD) risk in diabetic women. Dyslipidemia, which represents a series of lipid metabolism disorder, plays a role in the development of atherosclerotic cardiovascular diseases. In the present study, there was a significant decrease in BMI, HDL cholesterol and oestrogen levels in premenopausal diabetic women compared with women with 3 parity. Although, there was a significant decrease in LDL cholesterol between diabetic subjects with 4-5 parity and their premenopausal counterparts. This in a way shows that multiparous diabetic women are more likely to have cardio protective properties than diabetic women with lower parity, as shown in this study with a statistically significant decrease (p=0.032) in LDL in women with 4-5 parities, when compared with pre-menopausal women. Also, there was a significantly increased (p=0.000) levels of estradiol which is known to have cardio-protective effect. There was also a sharp rise in oestrogen levels as parity increases. In a related study it was observed that the number of children was positively associated with body mass index and waist-hip ratio in both sexes. In women but not in men, number of children was inversely associated with high-density lipoprotein cholesterol and was positively associated with triglycerides and diabetes [25]. Another study conducted in China in 2016 suggests that parity could correlate with lipid metabolism in Chinese women. Individuals with higher parity appeared to have a lower total cholesterol in blood, [26]. Although, in this study, there was no significant difference in total cholesterol between the levels of parities and premenopausal diabetic women. However, HDL levels for 4-5 parity diabetic women was significantly higher than that of their premenopausal counterparts.

**CONCLUSION**

In conclusion, menopause in apparently healthy women is known according to previously published studies to increase most cardiovascular risks (decrease in HDL, increase in LDL cholesterol and a reduction in estrogen levels), that is a reduction in cardio protective effect due to reduction in estradiol levels. But this study, which assessed the changes in estradiol and lipid profile between pre-menopausal and post-menopausal diabetic women, found out that the above fact is reversed in diabetes. That is, post-menopausal women were observed to have significantly higher estradiol levels, lower HDL values and higher LDL/HDL ratio. This implies that in spite of the higher estradiol levels, its cardio protective effect is not manifested (lower HDL and higher LDL/HDL ratio), probably due to the complications of diabetes.

But it is difficult to assess the role of menopause independently of diabetes. The study has also shown that diabetic women with 3 and 4-5 parities have a significantly increased HDL cholesterol and an unchanged LDL-cholesterol levels. HbA1c levels were also found to reduce in 3 and 4-5 parities diabetic women when compared with pre-menopausal women. There was also a dramatic increase in estrogen levels.

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