International Journal of Scientific Reports
*Diaf M et al. Int J Sci Rep. 2016 Oct;2(10):258-264*
http://www.sci-rep.com
pISSN 2454-2156 | eISSN 2454-2164

DOI: http://dx.doi.org/10.18203/issn.2454-2156.IntJSciRep20163397

**Original Research Article**

# Factors influencing atherogenic indices in type 2 diabetic women in northwestern Algeria

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**Received:** 30 July 2016
**Accepted:** 31 August 2016

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## ABSTRACT

**Background:** Type 2 diabetic women are at higher risk of developing atherogenic dyslipidemia. The major possible risk factors are obesity, abdominal fat accumulation and poor glycaemic control. However, menopause-related changes could be another determinant. The aim of this study was to evaluate the interrelationships of these risk factors and their independent effects on atherogenic indices in type 2 diabetes women.
**Methods:** A prospective, cross-sectional study, which includes 160 women agreed to participate in this study. Anthropometrics, biochemical parameters and blood pressure were measured. Atherogenic indices - total cholesterol-to-high-density lipoprotein cholesterol ratio (TC/HDL) and apolipoprotein (apo) B-to-apo A1 ratio, were calculated. Individual risk factors were examined in relationship to these atherogenic indices using correlation tests and logistic regression.
**Results:** 23.12% of the participants were normal weight and 76.87% were overweight/obese. The overall mean age was 57.70±11.16 years. Diabetes duration (>5years), anthropometric parameters, poor glycaemic control, high apo B and high level of low-density lipoprotein (LDL) were found to be significant determinants of atherogenic indices changes. The TC/HDL ratio was weakly associated with both BMI and waist circumference. However, the apo B/apo A1 ratio provided positive correlations with anthropometric parameters, especially with waist circumference ($p$=0.185, r=0.108, $r^2$=0.012), and this, in both pre and post-menopausal type 2 diabetic women.
**Conclusions:** The atherogenic risk, estimated by TC/HDL and apo B/apo A1 ratios, becomes more severe with higher anthropometric parameters (BMI and waist circumference), diabetes duration and poor glycaemic control in type 2 diabetes women and this during both premenopausal and postmenopausal periods.

**Keywords:** Type 2 diabetes, Atherogenic indices, Risk factors, Women, Anthropometric parameters

## INTRODUCTION

Type 2 diabetes (T2D) has now become a global public health burden affecting all strata of societies in both developed and developing countries, it is a well-known risk factor in the incidence of cardiovascular disease (CVD) and atherogenic dyslipidemia.[1] The atherogenic dyslipidemia, a common metabolic disorder, is characterized by elevated very low density lipoprotein (VLDL), small dense low density lipoprotein (LDL) and low high density lipoprotein (HDL) levels, which constitute the lipid triad and are considered as traditional risk factors for cardiovascular events.[2] Recently, lipoproteins and apolipoproteins (apo) ratios have also been found as consistent predictors of atherogenic risk than lipids alone.[3] Therefore, the mosaic of modifiable CVD risk issues imply some physiological factors which include the untreated hypertension and high toal cholesterol level, as well as the increased prevalence of sedentary, the overall and/or abdominal obesity and insulin-resistant, these latter may also vary according to ethnicity, age and gender.[3,4]

In women, comparing to men, manifest symptoms of CVD are generally delayed by approximately 10 to 15 years.[5] Scientists suggest that women benefit from the protective effects of ovarian hormones during the premenopausal period, however, men are more likely to be engaged in health-damaging behaviours.[6]

Biochemical, structural and physiological changes are due to the decreased in oestrogen levels during and after menopause, which alter the general health status of the woman. Oestrogen is known as an anti-atherogenic that could protect females against coronary artery disease during the premenopausal period. The post-menopausal women have less cardiovascular friendly lipid profiles than premenopausal ones.[7]

Hence, the aim of the present study was to assess the powerful factors that may influence on atherogenic indices (total cholesterol/HDL and apo B/apo A1) in type 2 diabetic women. We investigated the correlations between anthropometric parameters and atherogenic indices during both pre- and post-menopausal states.

## METHODS

### *Patients data*

One hundred sixty adult female subject with confirmed T2D for at least six months were recruited from April to September 2015, at the level of the Public Establishment of Proximity Health in Sidi-Bel-Abbes city (North-western Algeria).

Informed consent was obtained from all participants and ethical clearance was obtained from the relevant authority. We randomly solicited all adult women who met the inclusion criteria, that is, aged more than twenty, having T2D duration of less than fifteen years and exclusively under diet or oral anti-diabetic treatment, to participate in the study. However, pregnant and breastfeeding women as well as female patients with primary hyperlipidaemia, hypothyroidism, a confirmed cardiovascular disease, renal impairment or liver dysfunction were excluded from our study. Likewise, women using lipid-lowering drugs or who were treated with insulin have also been excluded.

Anthropometric measurements were taken during mornings according to the recommendations of the World Health Organization (WHO).[8] The electronic balance TS-2003A:360 lb (capacity: 180 kg, graduations 0.1 kg) was used for evaluating body weight (in kilograms) and the Seca 206 body meter (measuring range 0-220 cm, graduation length 1 mm) was employed for height measurement. The body mass index (BMI) was calculated as weight (kg)/height$^2$ (m$^2$).

The waist circumference was measured with a measuring tape (maximum: 150 cm, graduation length: 1 mm) which is tightened around the patient's abdomen, above the line passing through the navel, without depressing the skin.

### *Blood pressure measurement*

The morning blood pressure was evaluated using OMRON M3 Digital Automatic Blood Pressure Monitor (Omron Healthcare., Ltd. Kyoto, Japan), this sphygmomanometer can determine systolic blood pressures between 3-24 cm Hg, diastolic 1-21 cm Hg and heart rate 40-200 beats per minute.

### *Laboratory data*

Fasting blood samples (12 h after an overnight fast) were collected under aseptic conditions by venopuncture from the antecubital vein, into sterile plain tubes. The serum was used for the analysis of fasting glycaemia, total cholesterol (TC), HDL, LDL and triglycerides (TG) using the enzymatic colorimetric methods (Spinreact Reagents, Spain). Apo A1 and Apo B were quantified by turbidimetric tests (Spinreact Reagents, Spain). However, the glycosylated haemoglobin (HbA1c) concentration value was determined on fasting plasma samples using an ion exchange resin separation method.

### *Statistical analysis*

All data were processed and analysed through SPSS 23.0 (Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL. March 2015). Results are expressed as mean±standard deviations, the independent student t-test was used for comparing results between groups according to the women corpulence.

Binary logistic regression was used in order to determine the factors associated with atherogenic indices, results are presented using odds ratios with a 95% confidence interval (95% CI). A *p*-value lower than 0.05 was considered statistically significant for all statistical tests. Relationships between lipids, apolipoproteins ratios and anthropometric parameters were studied using Pearson correlation tests and simple linear regression tests with a confidence interval of 95%.

## RESULTS

Table 1 displays the subjects' characteristics. Amongst all patients, 23.12% were normal weight and 76.87% were either overweight or obese. The overall mean age was 57.70±11.16 years (56.00±14.20 years in normal weight and 58.24±11.57 years in overweight/obese), with no significant differences between the two groups. However, we noted a high significant difference of height and waist circumference ($p < 0.01$). No differences between the two groups was observed with respect to age, diabetes duration, blood pressure and all the studied conventional biochemical parameters. Comparing TC/HDL and apo B/apo A1 ratios between normal weight and overweight/

obese women, no significant differences were noted. Nevertheless, an exception was found for TC/HDL ratio during the pre-menopausal period (p =0.005). As illustrated in Table 2, we investigated risk factors associated with elevated TC/HDL ratio (≥3) levels.

The performed logistic regression analysis indicated that the pathological atherogenic index (TC/HDL ≥3) was significantly associated with diabetes duration (>5 years), overweight, poor glycaemic control (HbA1c >7%), and high apo B and LDL levels.

**Table 1: Characteristics of the studied cases.**

| Variables | All patients | Normal weight | Overweight/obese | P value for Student t-test* |
|---|---|---|---|---|
| **N (%)** | 160 | 37 (23.12) | 123 (76.87) | - |
| **Age (Years), Means±S.D** | 57.70±11.16 | 56.00±14.20 | 58.24±11.57 | 0.381 |
| **Duration of diabetes (years), Means±S.D** | 7.04±3.85 | 6.27±3.79 | 6.71±4.01 | 0.579 |
| **Anthropometric characteristics, (Means±S.D)** | | | | |
| **Weight (kg)** | 73.84±11.82 | 63.59±6.07 | 69.68±7.39 | <0.001 |
| **Height (cm)** | 160.91±6.80 | 164.13±6.01 | 159.60±7.36 | 0.002 |
| **Waist circumference (cm)** | 97.78±14.14 | 86.20±10.37 | 95.93±9.93 | <0.001 |
| **BMI (kg/m$^2$)** | 28.49±4.43 | 23.56±1.20 | 27.10±1.38 | <0.001 |
| **Overweight, obesity duration (years)** | - | - | 9.31±6.25 | - |
| **Blood pressure, Means±S.D** | | | | |
| Systolic pressure (mmHg) | 12.90±1.48 | 12.62±1.18 | 13.09±1.60 | 0.123 |
| Diastolic pressure (mmHg) | 7.60±0.98 | 7.54±1.02 | 7.60±1.01 | 0.760 |
| **Menopausal status, n (%)** | | | | |
| Pre-menopause | 49 (30.6) | 12 (7.5) | 37 (23.1) | - |
| Oestrogen use (yes) | 39 (24.35) | 12 (7.5) | 27 (16.85) | - |
| Oestrogen use (no) | 10 (6.24) | - | 10 (6.25) | - |
| Post-menopause | 111 (69.4) | 25 (15.6) | 86 (53.8) | - |
| **Menopausal age (years)** | | | | |
| Pre-menopause | 45.55±9.70 | 40.00±12.52 | 47.35±7.99 | 0.021 |
| Post-menopause | 63.06±6.66 | 63.68±6.41 | 62.88±6.76 | 0.604 |
| **Biochemical parameters (g/L)** | | | | |
| **Fasting glycaemia** | 1.53±0.61 | 1.47±0.54 | 1.58±0.65 | 0.419 |
| **Postprandial glycaemia** | 2.26±0.96 | 2.33±0.92 | 2.26±0.93 | 0.696 |
| **HbA1c** | 7.70±1.30 | 7.96±1.39 | 7.64±1.29 | 0.255 |
| **Fasting TC** | 1.70±0.35 | 1.72±0.31 | 1.66±0.36 | 0.466 |
| **Fasting HDL-c** | 0.40±0.11 | 0.39±0.13 | 0.40±0.11 | 0.695 |
| **Fasting LDL-c** | 1.07±0.32 | 1.16±0.29 | 1.04±0.33 | 0.092 |
| **Fasting TG** | 1.50±0.76 | 1.44±0.82 | 1.45±0.72 | 0.922 |
| **Apo A1** | 1.33±0.36 | 1.26±0.27 | 1.38±0.40 | 0.150 |
| **Apo B** | 0.99±0.46 | 0.92±0.32 | 1.00±0.52 | 0.418 |
| **TC/HDL-c** | 4.52±1.47 | 4.89±2.00 | 4.42±1.27 | 0.101 |
| **TC/HDL-c during pre-menopause** | 4.38±1.62 | 5.62±2.25 | 3.83±1.05 | 0.005 |
| **TC/HDL-c during post-menopause** | 4.59±1.40 | 4.49±1.77 | 4.61±1.32 | 0.761 |
| **Apo B/Apo A1** | 0.77±0.35 | 0.75±0.29 | 0.78±0.36 | 0.691 |
| **Apo B/Apo A1 during pre-menopause** | 0.71±0.32 | 0.81±0.41 | 0.64±0.28 | 0.168 |
| **Apo B/Apo A1 during post-menopause** | 0.79±0.36 | 0.71±0.21 | 0.79±0.39 | 0.380 |

*Comparison of means, between normal weight patients and overweight/obese ones. BMI: body mass index. HbA1c: glycosylated haemoglobin. TC: total cholesterol. HDL-c: high density lipoprotein cholesterol. LDL-c: low density lipoprotein cholesterol. TG: triglycerides. Apo: apolipoproteins.

**Table 2: Crude odds ratio of risk factors associated with TC/HDL levels.**

| Risk factors | TC/HDL-c < 3 | TC/HDL-c ≥ 3 | Odd ratio (95% CI OR) | P* |
|---|---|---|---|---|
| | Number (%) | Number (%) | | |
| **Age** | | | | |
| <40 years | 3 (1.9) | 7 (4.4) | Reference | |
| 40-60 years | 11 (6.9) | 58 (36.2) | 0.200 [0.017-2.303] | 0.197 |
| >60 years | 9 (5.6) | 72 (45.0) | 0.687 [0.147-3.215] | 0.633 |
| **Diabetes duration** | | | | |
| < 5 years | 5 (3.1) | 43 (26.9) | Reference | |
| 5-10 years | 13 (8.1) | 49 (30.6) | 1.500 [0.304-7.409] | 0.019 |
| > 10 years | 5 (3.1) | 45 (28.1) | 0.590 [0.159-2.193] | 0.431 |
| **BMI** | | | | |
| <25 kg/m$^2$ | 6 (3.8) | 31 (19.4) | Reference | |
| 25-29.9 kg/m$^2$ | 11 (6.9) | 58 (36.2) | 1.098 [0.118-10.226] | 0.034 |
| ≥30 kg/m$^2$ | 6 (3.8) | 48 (30.0) | 0.972 [0.264-3.578] | 0.966 |
| **Waist circumference** | | | | |
| ≤80 cm | 5 (3.1) | 20 (12.5) | Reference | |
| >80 cm | 18 (11.2) | 117 (73.1) | 0.605 [0.071-5.144] | 0.645 |
| **Menopausal status** | | | | |
| Pre-menopause | 10 (6.2) | 39 (24.4) | Reference | |
| Post-menopause | 13 (8.1) | 98 (61.2) | 1.021 [0.201-4.969] | 0.865 |
| **HbA1c level** | | | | |
| ≤ 7% (53.01mmol/mol) | 1 (0.6) | 52 (32.5) | Reference | |
| > 7% (53.01mmol/mol) | 22 (13.8) | 85 (53.1) | 1.257 [0.155-10.978] | 0.018 |
| **Apo B level (0.9 g/L)** | | | | |
| Normal range | 18 (11.2) | 61 (38.1) | Reference | |
| Below normal range | 5 (3.1) | 76 (47.5) | 1.227 [1.067-1.770] | 0.017 |
| **LDL-c level (0.8 g/L)** | | | | |
| Normal range | 18 (11.2) | 55 (34.4) | Reference | |
| Below normal range | 5 (3.1) | 82 (51.2) | 1.231 [1.071-1.746] | 0.014 |

*multivariate logistic regression significant at $p$=0.05. CI: confidence interval. OR: odd ratio. BMI: body mass index. TC: total cholesterol. HbA1c: glycosylated haemoglobin. Apo B: apolipoproteine B. LDL-c: low-density lipoprotein cholesterol.

The odds ratios of having a high TC/HDL ratio were 1.098 [0.0118-10.226] and 1.000 [0.201-4.969] in overweight and post-menopausal women, respectively. Female subjects with poor glycaemic control (HbA1c >7%) were 1.257 [0.155-10.978] times more at risk of having a higher atherogenic index (TC/HDL).

Our results about risk factors associated with high apo B/apo A1 ratio (>0.7) are summarised in Table 3. The logistic regression analysis showed that higher apo B/apo A1 ratios are associated with diabetes duration (>5 years), abdominal obesity, poor glycaemic control (HbA1c >7%), post-menopausal period and high LDL levels. The odds ratios of having an apo B/apo A1 >7 was 1.504 [0.528-4.284] in patients with more than five years of diabetes, 1.976 [0.538-7.259] in those suffering from abdominal obesity and 1.239 [0.364-4.219] in post-menopausal women.

As depicted in Figure 1, the TC/HDL ratio was weakly associated with both BMI and waist circumference. However, the apo B/apo A1 ratio provided positive correlations with anthropometric parameters, especially with waist circumference ($p$ =0.185, r =0.108, r$^2$ =0.012) in both pre- and post-menopausal type 2 diabetic women.

## DISCUSSION

The association between altered lipid profile and atherosclerotic cardiovascular events is becoming more accepted in postmenopausal women, despite that some observed metabolic/physiological changes may occur as results of aging.[9,10] However, menopause tends to be associated with an increased risk of general obesity, abdominal fat distribution and associated health risk factors.[11]

In the present study, we aimed to assess factors influencing atherogenic indices in T2D women, during premenopausal and postmenopausal periods. Furthermore, to investigate correlations between overall obesity (estimated by BMI), abdominal fat accumulation (estimated by waist circumference) and atherogenic indices (TC/HDL and apo B/apo A1).

**Table 3: Crude odds ratio of risk factors associated with Apo B/Apo A1 levels.**

| Risk factors | Apo B/Apo A1 < 0.7 | Apo B/Apo A1 ≥ 0.7 | Odd ratio (95% CI OR) | P* |
|---|---|---|---|---|
| | Number (%) | Number (%) | | |
| **Age** | | | | |
| <40 years | 6 (3.8) | 4 (2.5) | Reference | |
| 40-60 years | 37 (23.1) | 32 (20.0) | 0.588 [0.080-4.327] | 0.602 |
| >60 years | 41 (25.6) | 40 (25.0) | 0.776 [0.271-2.227] | 0.637 |
| **Diabetes duration** | | | | |
| < 5 years | 22 (13.8) | 26 (16.2) | Reference | |
| 5-10 years | 37 (23.1) | 25 (15.6) | 1.504 [0.528-4.284] | 0.045 |
| > 10 years | 25 (15.6) | 25 (15.6) | 0.555 [0.215-1.430] | 0.223 |
| **BMI** | | | | |
| <25 kg/m$^2$ | 20 (12.5) | 17 (10.6) | Reference | |
| 25-29.9 kg/m$^2$ | 37 (23.1) | 32 (20.0) | 0.638 [0.184-2.215] | 0.479 |
| ≥30 kg/m$^2$ | 27 (16.9) | 27 (16.9) | 0.780 [0.315-1.931] | 0.591 |
| **Waist circumference** | | | | |
| ≤80 cm | 14 (8.8) | 11 (6.9) | Reference | |
| >80 cm | 70 (43.8) | 65 (40.6) | 1.976 [0.538-7.259] | 0.030 |
| **Menopausal status** | | | | |
| Pre-menopause | 29 (18.1) | 20 (12.5) | Reference | |
| Post-menopause | 55 (34.4) | 56 (35.0) | 1.239 [0.364-4.219] | 0.731 |
| **HbA1c level** | | | | |
| ≤ 7% (53.01mmol/mol) | 26 (16.2) | 27 (16.9) | Reference | |
| > 7% (53.01mmol/mol) | 58 (36.2) | 49 (30.6) | 1.042 [0.469-2.315] | 0.020 |
| **Apo B level (0.9 g/L)** | | | | |
| Normal range | 62 (38.8) | 17 (10.6) | Reference | |
| Below normal range | 22 (13.8) | 76 (47.5) | 0.079 [0.034-0.183] | <0.001 |
| **LDL-c level (0.8g/L)** | | | | |
| Normal range | 46 (28.8) | 27 (16.9) | Reference | |
| Below normal range | 38 (23.8) | 49 (30.6) | 1.327 [1.242-1.144] | 0.015 |

*multivariate logistic regression significant at $p$=0.05. CI: confidence interval. OR: odd ratio. BMI: body mass index. Apo A1: apolipoproteine A1. HbA1c: glycosylated haemoglobin. Apo B: apolipoproteine B. LDL-c: low-density lipoprotein cholesterol.

Results from this study revealed higher levels of TC/HDL and apo B/apo A1 in all female subjects, indicating that all of our patients are prone to an increased cardiovascular risk. Furthermore, when adapting our apo B/apo A1 data with AMORIS and INTERHEART thresholds, almost 36% of all participants were at high myocardial infarction risk.[12,13]

In our female subjects, the TC/HDL ratio was significantly influenced by overall obesity, poor glycaemic control, apo B and LDL levels. According to Stępień et al, in patients with T2D, the TC/HDL ratio is considered as a cumulative marker of cardiovascular risk.[14] However, this ratio is not stable, it is modified by several factors including BMI, food intake and the time of blood sampling.[15] Despite that the BMI is a good indicator of body fat degree, it however does not capture body fat distribution, which the waist circumference dose. Intriguingly, the apo B/apo A1 ratio was more likely to be associated with abdominal obesity, poor glycaemic control and LDL level. According to many studies, the apo B/apo A1 seems to be an effective predictor of coronary heart disease risk in overweight and obese individuals.[12,13,16,17]

The apolipoproteins are slightly influenced by meals and biological variables, unlike the ordinary lipid parameters, which fluctuate widely depending on food intake.[3] Therefore, measurement of apolipoproteins does not require fasting blood samples, which represent a main advantage.

In T2D patients, glycaemic control via the HbA1c is considered as the backbone in the management of diabetes.[18] An increase of one percent in HbA1c level above the accepted threshold of 7% is equivalent to a

change of about 30 mg/dl in mean plasma glucose.[19] Thus, the cardio-metabolic risk of our patients is compounded by the problem of poor glycaemic control.

Regarding menopausal status, our results indicate that the post-menopausal stage is associated with increased atherogenic indices (TC/HDL and apo B/apo A1) without however being significant.

During the transition from pre-menopause to menopause and post-menopause, the central deposition of fat is determined by specific genetic factors and leads to metabolic correlated changes, including the risk of cardiovascular diseases. The oestrogenic depletion after menopause is associated with changes in body fat distribution. As a result, a decrease in sex hormone binding globulin is noted, and an increase of free androgen level leads to higher androgenicity.[20] Hormone Replacement Therapy can prevent the central distribution of fat, which explains the role of sex hormones.

The correlation tests through this investigation noticeably showed, during both premenopausal and postmenopausal periods, that the apo B/apo A1 ratio was marginally related to the BMI ($r^2$ =0.002, F =0.320, p =0573). However, although not significant, the apo B/apo A1 was positively correlated with waist circumference ($r^2$ =0.012, F =1.770, p =0.185). On the other hand, the TC/HDL ratio was faintly associated to anthropometric parameters in both pre and post-menopausal women.

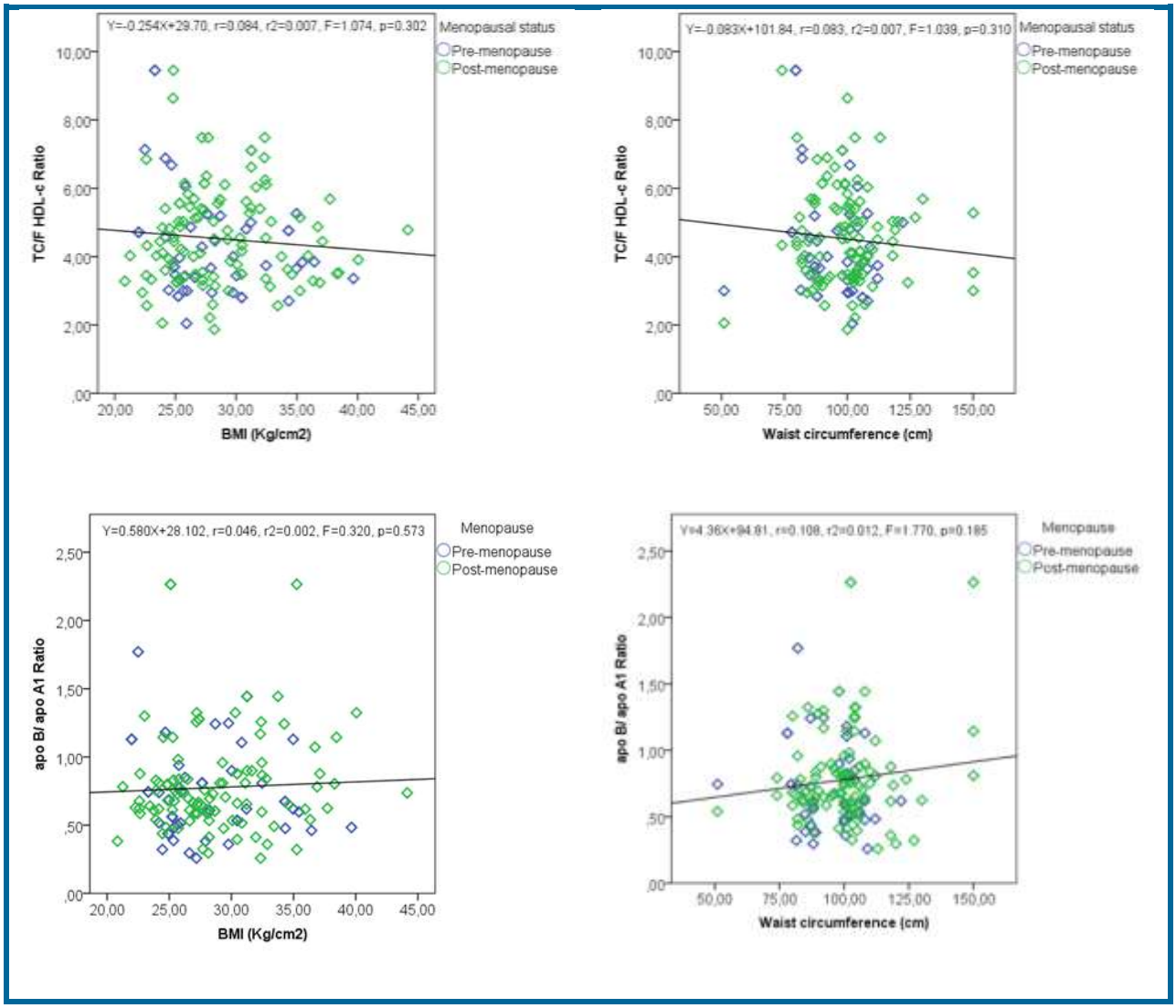


**Figure 1: Association between TC/HDL-c and Apo B/Apo A1 ratios and body parameters according to the menopausal status.**

## CONCLUSION

The atherogenic risk, one of the CVD risk factors, estimated by index ratios (TC/HDL and apo B/apo A1), becomes more severe with higher anthropometric parameters including BMI and more specifically the waist circumference. However, the poor glycaemic control depicts another parameter that could influence the atherogenicity in T2D women and this during both premenopausal and postmenopausal periods. As apolipoproteins can be analysed in non-fasting samples, it is of great practical advantage for patients and doctors to use apo B/apo A1 ratio as an indicator of atherosclerosis. It could be very helpful to use a single ratio for risk prediction instead of referring to a larger number of lipid ratios. The apo B/apo A1 ratio is more correlated to waist circumference than BMI, this last depends upon the individual's physical activity and lifestyle conditions.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the institutional ethics committee*

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**Cite this article as:** Diaf M, Khaled BM. Factors influencing atherogenic indices in type 2 diabetic women in northwestern Algeria. Int J Sci Rep 2016;2(10):258-64.