

# Hematocrit and mean arterial blood pressure in pre- and postmenopause women

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**Abstract:** The relationship between mean arterial blood pressure (*MAP*) and hematocrit (*Hct*) was studied in pre- and postmenopause women in the city of Durango, Mexico. Premenopause women show a negative trend between parameters that is not statistically significant. *MAP* and *Hct* are directly related in postmenopause women ( $p < 0.01$ ). It is proposed that this *MAP/Hct* relationship is in part due to differences in endothelial function where menopause decreases the capacity of the endothelium to respond to increased blood viscosity and shears stress, leading to the increased production of vasodilator mediators to compensate for changes in blood viscosity due to changes in *Hct*. Comparison with a large group of postmenopause women in the city of Stockholm showed identical trends.

**Keywords:** menopause, endothelial dysfunction, blood viscosity, blood pressure, hematocrit

## Introduction

Postmenopausal women have an increased risk of cardiovascular disease in comparison to premenopausal women, which increases with age. This risk is associated with the incidence of hypertension, smoking, obesity, sedentary life style, dyslipidemia, stress, family history of cardiovascular disease, diabetes mellitus, insulin resistance, changes in body fat distribution from a gynoid to an android pattern, reduced glucose tolerance, abnormal plasma lipids, increased sympathetic tone, vascular inflammation, and endothelial dysfunction.<sup>1</sup>

Endothelial dysfunction is increasingly recognized as a condition that may underlie most metabolic and endocrine diseases that result in cardiovascular risks. Maturana and colleagues<sup>2</sup> summarized the changes in endothelial function determined by the transition from pre- to postmenopause and discussed methods presently available for assessing endothelial function. These methods in general evaluate how the circulation responds to acute vasoactive stimuli mediated by endothelial mechanisms.<sup>3,4</sup>

A different approach for characterizing endothelial dysfunction consists in studying the population has analyzing parameters that are in part dependant on endothelial function. One of these associations is given by the relationship between mean arterial blood pressure (*MAP*) and blood viscosity or the related hematocrit (*Hct*).<sup>5</sup>

Blood viscosity and *MAP* are related by the interaction of two opposing mechanisms. Firstly, increasing *Hct* increases blood viscosity and peripheral vascular resistance, and therefore *MAP*. Secondly, increasing blood viscosity increases shear stress on the endothelium and therefore the production of endothelial nitric oxide (NO) causing vasodilatation.<sup>6</sup> These two opposing effects lead to an autoregulatory mechanism that

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tends to maintain peripheral vascular resistance and therefore *MAP* stays constant in response to changes of blood shear stress, blood viscosity, and *Hct*.

Hematocrit and therefore blood viscosity present a natural variability in the population due to adaptations to altitude, genetics, diet, and level of exercise performed. However the relation between *MAP* and *Hct* in the healthy population (not afflicted by endothelial dysfunction) should be independent of *Hct* as a consequence of the above mentioned autoregulatory process, as well as additional blood pressure regulating mechanism. Maturana and colleagues<sup>2</sup> summarized the changes in endothelial function determined by the transition from pre- to postmenopause, showing differences that could in principle lead to different relationships between *MAP* and *Hct*, which can also be due to the difference in hormonal conditions.

The present study analyzes the distribution of *MAP* and *Hct* in a population of pre- and postmenopause women from the city of Durango, Mexico (elevation 1,890 m), a population with similar ethnic characteristics and approximately uniform environmental and dietary features to determine if the relationship between *MAP* and *Hct* shows evidence of changes of the autoregulatory capacity of endothelial function in maintaining *MAP* independent of *Hct* in both groups. The availability of a large data pool from a population of postmenopausal women from the city of Stockholm, Sweden (sea level) also provided the opportunity to establish whether findings from the Mexican population were unique and due to local characteristics or could be attributed to a more general process associated with menopause and possibly endothelial dysfunction.

## Methods

The study was carried out at the Institute for Research of the Universidad Juarez del Estado de Durango (UEJD). Individuals were entered following open invitations to non-hypertensive and nondiabetic women that visit the Institute to obtain their Papanicolaou test. The study was transversal and descriptive. Exclusion criteria were women during their menstrual period, smoking, the use of contraceptives, and any type of treatment including treatment for hypertension. Inclusion criteria were pre- and postmenopause women without age limitation. Women were determined to be in good health conditions on the basis of medical records and clinical investigation. Postmenopause women were not treated for hormonal therapy within at least three months prior to entering the study.

The protocol was approved by the UEJD Research Committee and informed consent was provided by each

individual. The study was carried out according to laws and regulations of the General Health Law of Mexico. A written survey was carried out to determine the level of sedentariness of the participants; individuals that did not perform at least 30 minutes of intense exercise five days per week were excluded.

Laboratory analysis included fasting glucose, urea, creatinine, and *Hct*. Blood samples (3 ml) were drawn in tubes without anticoagulants from the antecubital vein, 8 to 10 h after fasting and collected in EDTA anticoagulated tubes for *Hct* measurements. *Hct* was measured using a microhematocrit centrifuge (13,000 g for 3 min at 20 °C, Sol-Bat Centrifuge M-600, Readacrit L-10, Mexico).

Systolic and diastolic pressures were recorded and *MAP* was determined using the relationship:

$$MAP = P_{diastolic} + 1/3(P_{systolic} - P_{diastolic}).$$

Blood samples and *MAP* measurements were obtained at random times in between the menstrual periods.

The data was also analyzed by a method that (approximately) factors out the contribution of blood viscosity to peripheral vascular resistance,<sup>7</sup> thus providing information on the relative state of constriction or relaxation of circulation, corresponding to the contribution of the anatomical component of vascular resistance in the configuration of total peripheral vascular resistance. This procedure consists in calculating a *Hct*-independent *MAP<sub>i</sub>* according to the algorithm:

$$MAP_i = MAP_{m,i} \frac{Hct_{average}}{Hct_i} \quad (1)$$

where *MAP<sub>m,i</sub>* is the measured value, *Hct<sub>average</sub>* is the average for the sample population, and *Hct<sub>i</sub>* is the *Hct* associated with a given pressure measurement.

## Statistical analysis

All parameters are reported as mean ± standard deviation (SD). Differences between groups were assessed using the paired Student *t*-test. A *P* value of <0.05 defined the level of statistical significance. Linear regression analysis was carried out using the Prism program.

## Results

Results are reported in Table 1. The only statistical difference between groups was *MAP*, which was significantly (*P* < 0.005) elevated in postmenopause women, but did not reach the level of hypertension.

**Table 1** Population features, blood chemistry, Hct and MAP of pre- and postmenopause women

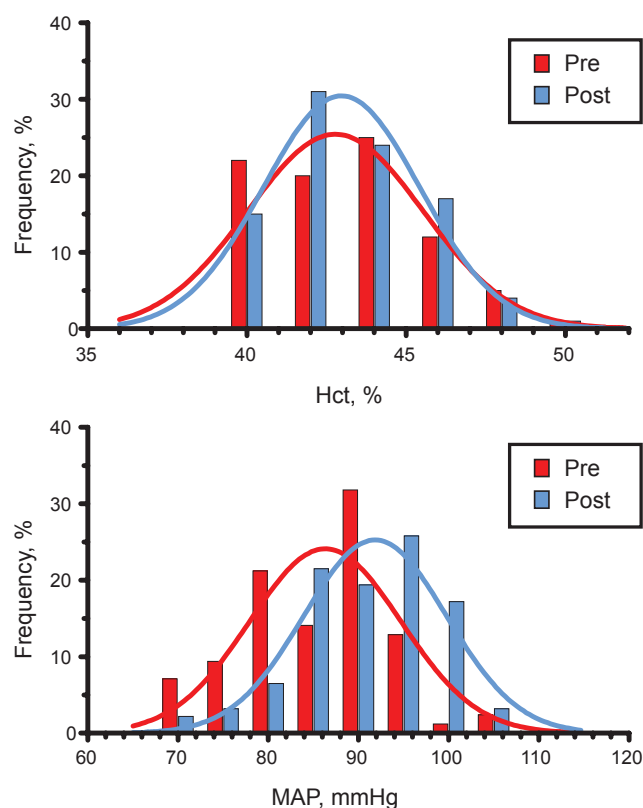
	Premenopause	Postmenopause
Number, n	85	92
Age, years	39.2 ± 3.3	52.1 ± 7.2
Hematocrit, %	42.6 ± 2.4	42.9 ± 2.3
Mean arterial blood pressure, mmHg	85.6 ± 7.7*	89.8 ± 11.0*
Weight, kg	66.9 ± 10.3	67.7 ± 10.0
BMI	26.5 ± 3.9	27.6 ± 5.3
Urea, mg/dl	22.3 ± 2.5	23.1 ± 2.4
Creatinine, mg/dl	0.77 ± 0.10	0.75 ± 0.12
Glucose, mg/dl	90.5 ± 2.5	92.1 ± 9.0

**Notes:** \*Statistically different between groups,  $p < 0.005$ .

**Abbreviations:** BMI, body mass index; Hct, hematocrit; MAP, mean arterial blood pressure.

The statistical distribution of *Hct* in the two groups is shown in Figure 1, showing a lack of statistically significant difference.

The relation between *MAP* and *Hct* was investigated by computing the linear dependence between these variables. *MAP* was linearly and significantly related to *Hct* with

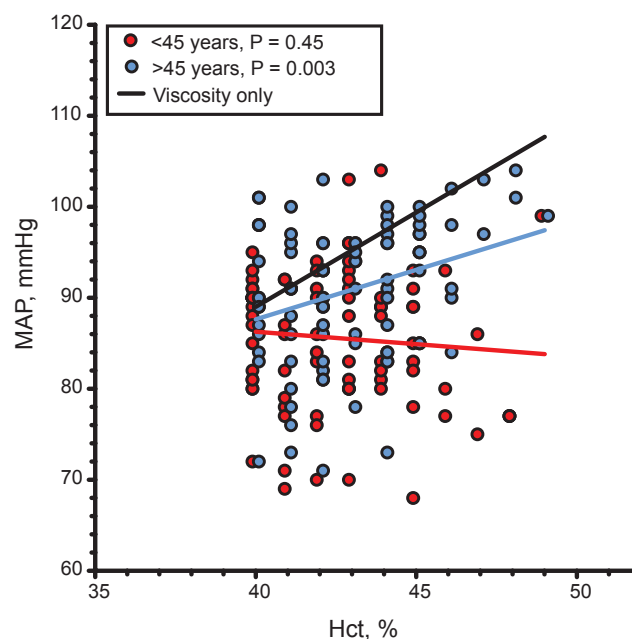
**Figure 1** Distribution of hematocrit (Hct) and mean arterial blood pressure (MAP) in pre- and postmenopausal women in the city of Durango, Mexico. Both distributions are Gaussian.

a positive slope  $m = 1.09 \pm 0.35$  mmHg/%,  $p < 0.01$  in postmenopause women. The same analysis for premenopause women showed a negative correlation with a slope  $m = -0.27 \pm 0.36$  mmHg/%,  $p = 0.5$  which was not statistically significant. However the difference between slopes was statistically significant,  $p < 0.01$ . This analysis is shown in Figure 2.

The relationship between *MAP* normalized relative to *Hct* and *Hct* had a negative slope for both pre- and postmenopause women ( $-2.14 \pm 0.34$  and  $-1.02 \pm 0.34$  mmHg/%,  $p < 0.005$  for both cases, respectively). The difference between slopes was also significant ( $p < 0.02$ ).

## Discussion

The principal findings of this study are that pre- and postmenopause women did not present a significant difference in blood analysis, *Hct* and weight, with the exception of blood pressure which was significantly ( $p < 0.005$ ) elevated in the postmenopause women. However, none of the postmenopausal women was diagnosed hypertensive and therefore received no antihypertensive treatment. As expected, *Hct* presented a variability in both populations, however the variability was identical, and the average *Hct* was not statically different between groups, a result supported by the findings of Clancy and colleagues.<sup>8</sup> Notably, altitude did not appear to be a factor in determining the average or dispersion of

**Figure 2** Linear regression between MAP and Hct in pre- and postmenopause women in the city of Durango, Mexico. Comparison with the relation between MAP and Hct if blood viscosity is the only determinant of peripheral vascular resistance.

**Abbreviations:** Hct, hematocrit; MAP, mean arterial blood pressure.

*Hct* in the population studied since pre- and postmenopause in Durango (elevation 1,890 m) had *Hct*  $42.6 \pm 2.4\%$  and  $42.9 \pm 2.3\%$ , respectively while white women in a study by de Simone and colleagues,<sup>5</sup> conducted in the city of New York, NY, aged  $53.8 \pm 12.1$  had *Hct*  $42 \pm 3\%$ . Similarly, body mass index was not different between these populations ( $p > 0.3$ , ns).

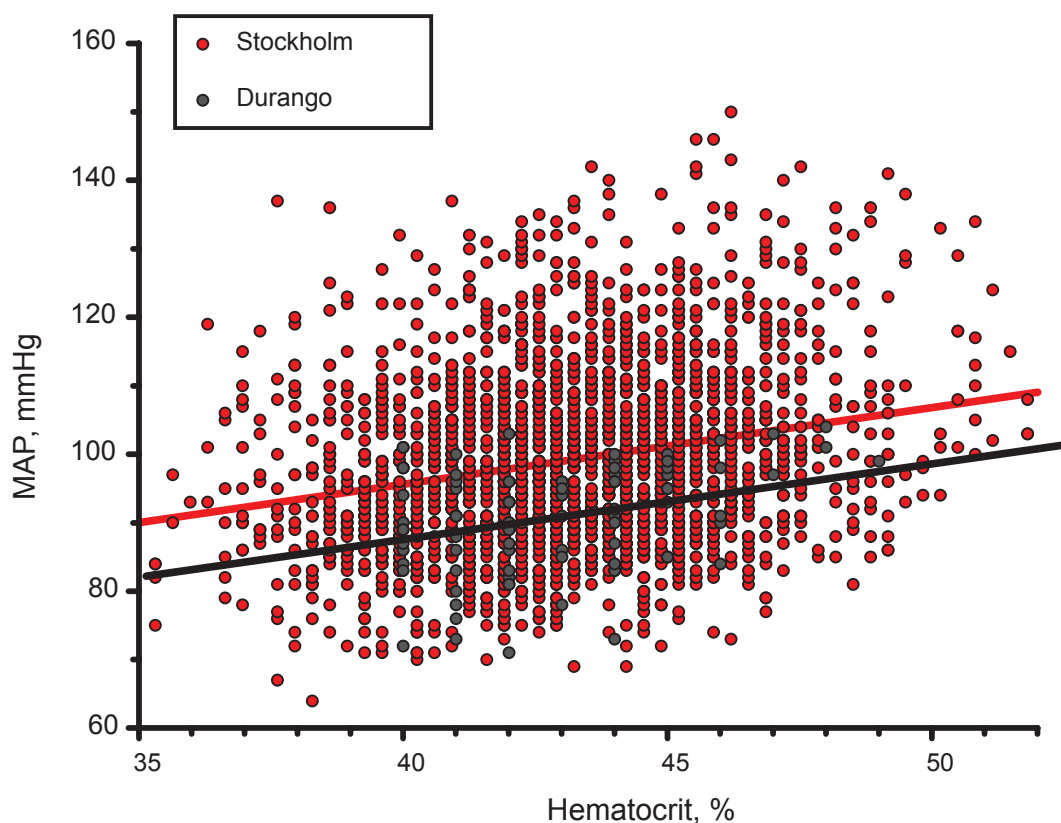
The distributions of *Hct* and *MAP* were Gaussian, allowing the calculation of the least square regression between parameters. The finding of the lack of positive correlation between *MAP* and *Hct* for premenopause women, and the tendency of the data to show a negative correlation is significant, since it suggests the operation of the previously discussed autoregulatory mechanism that renders *MAP* independent from the change in *Hct* and therefore presumably blood viscosity.

Figure 2 shows the change in blood pressure that would be present if the circulation responded passively to the changes of blood viscosity caused by changes in *Hct*. This calculation is made by assuming that the relation between *Hct* and blood viscosity in the range shown is linear, as shown by

the findings of Kameneva and colleagues.<sup>9</sup> The slope for this line is  $m = 2.08 \text{ mmHg}/\%$  being statistically different ( $p < 0.01$ ) from the slope of the line relating *MAP* and *Hct* for postmenopause women.

The finding that the theoretical slope for the change in *MAP* due solely to the change in *Hct* is greater than that found in this study suggests that the impairment of endothelial function leading to the increased *MAP* in postmenopause women is not complete, and that in general a residual autoregulatory capacity remains.

Information on the relationship between *MAP* and *Hct* is available from a study carried out in the city of Stockholm, Sweden in a population of  $n = 2,189$  women aged  $> 60$  years. The results of this comparison shown in Figure 3 is solely presented to show that populations present identical trends in the relationship between *MAP* and *Hct*, a result suggested by clinical<sup>10</sup> and experimental studies.<sup>6</sup> Notably the slopes of the two regression lines are virtually identical since the relationship for the Stockholm population has slope  $m = 1.12 \pm 0.09$  vs  $m = 1.09 \pm 0.35 \text{ mmHg}/\%$  for the population in Durango. Therefore a reduced capacity to regulate



**Figure 3** Comparison of the trends for *MAP* vs *Hct* for women aged  $> 60$  years in a study in the city of Stockholm ( $n = 2,189$ ) and postmenopause women in the city of Durango ( $n = 92$ ).

**Abbreviations:** *Hct*, hematocrit; *MAP*, mean arterial blood pressure.

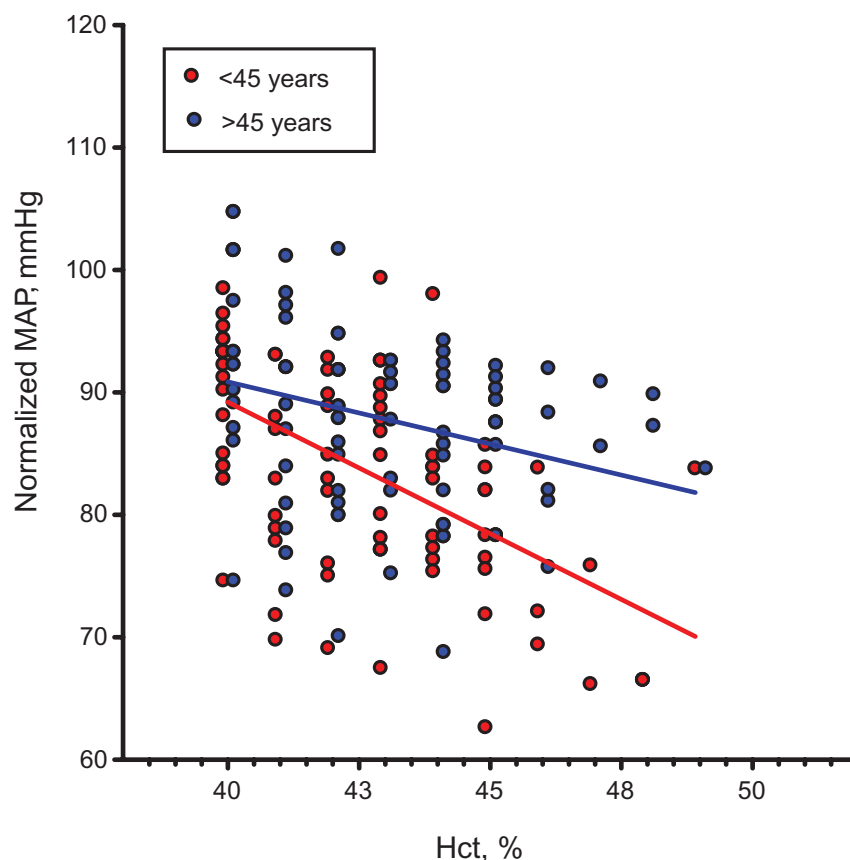
for the increase in *Hct* associated with menopause could be a characteristic for menopause. As expected, given the large number of subjects in the Stockholm group, the linear regression was significant ( $p < 0.0001$ ). These findings may also indicate that age *per se* may be a factor in lowering the capacity for autoregulation of *MAP* vs *Hct*, due to factors other than endothelial dysfunction.

It is generally assumed that elevated *Hcts* are associated with increased *MAP*, as shown by studies in chronic diseases such as hypertension and diabetes. However this does not necessarily obtain when changes in *Hct* are related to changes in peripheral vascular resistance, blood viscosity, and *MAP* as shown by de Simone and colleagues,<sup>11</sup> who found that *Hct* and *MAP* were statistically significantly negatively correlated in American Indians. Salazar Vázquez and colleagues<sup>10</sup> also showed that *MAP* and *Hct* have a “U” shaped relation in type 2 diabetics. Martini and colleagues<sup>6</sup> analyzed in experimental animals the effect of small acute changes of *Hct* similar to does due to the natural variability in the human population and found a “U” shaped relation between *Hct* and *MAP*.

Therefore in recent studies of various populations the increase in *Hct* is not uniformly associated with increased *MAP*, unless a threshold *Hct* is surmounted in which case red blood cell hemoglobin may become a sink for endothelium-derived NO.<sup>12</sup> Furthermore, the tendency of a negative slope for the *MAP* vs *Hct* relationship found in this study may be a general feature in the healthy population.

Blood pressure regulation is also dependant on baroreceptor activity and metabolic factors. Therefore it should be expected that *MAP* and *Hct* are not related in the healthy population, however this tight regulation could be disrupted as a consequence of the significant endocrinologic changes that result from the transition to menopause as shown by the consistently observed related significant increase in *MAP*.

Factoring out the effect of blood viscosity shows that the anatomical contribution of peripheral vascular resistance tends to decrease with increasing *Hct* and presumably blood viscosity (Figure 4), the relationship being attenuated for post- relative to premenopause. The same negative correlation was found in the population of the Stockholm



**Figure 4** Mean arterial pressure as a function of hematocrit (*Hct*), and therefore blood viscosity, when the effect of hematocrit is factored out (Normalized *MAP* according to equation 1) Both trends are statistically significant ( $p < 0.05$  for  $<45$  years and  $>45$  years) as well as the difference in trends ( $p < 0.02$ ).

**Abbreviation:** *MAP*, mean arterial blood pressure.



women, however the slope was significantly shallower, being  $-0.40 \pm 0.08$  mmHg/%, a finding that could be related to the greater age of this population. These findings support the contention that the endothelial vasodilator release is different in these populations, and that it tends to decrease with menopause and age although the evidence is not direct. This result also shows that while some of the *MAP* autoregulatory capacity is lost in postmenopause women, in healthy women the process is still effective since there is a significant tendency for *MAP* to lower as *Hct* increases.

## Conclusions

This study shows that the healthy population of women presents a variability of *Hct* that is not significantly reflected in the variability of blood pressure, which should be expected if peripheral vascular resistance is passively influenced by blood viscosity. The decreased regulation of *MAP* versus the naturally occurring variability on *Hct* for postmenopause women found in two different populations and the strong similarity in the relationship between *MAP* and *Hct* suggest that this is a common feature to postmenopause. However, while this is a tendency in the population there are individuals that do not present increased blood pressure as a consequence of increased *Hct*. If we assume that that this tendency is related to a decreased autoregulatory capacity due to decreased response to shear stress by the endothelium, it may be possible to differentiate between the incidence or absence of endothelial dysfunction in the otherwise healthy population. Finally, this study does not show that there is a significant change in *Hct* between pre- and postmenopause healthy women.

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