

A Association of occult chronic kidney disease with cardiovascular risk and their risk factors in university workers

Angélica Jimenez-Rosales^{1a}, Victoria Dominguez^{2b}, Gilberto Felipe Vázquez Anda^{2c}, Gerardo Huitrón Bravo^{2d}

1: Faculty of Chemistry, The Autonomous University of the State of Mexico, Paseo Colón esq. Paseo Tollocan. Toluca, Estado de México. México. Zip Code.50120. Tel: +52 (722) 2 17 51 90 and 2 1751. Fax:(01 722) 2 17 38 90

2: Centro de Investigación en Ciencias Medicas, Jesus Carranza No. 200 esq. Venustiano Carranza, Col. Universidad. Toluca, Estado of Mexico. Mexico. CP 50130.

a: Masters in Chemistry; b: Doctor in Sciences; c: Philosophy Doctor; d: Masters in clinical investigation

Corresponding author: Victoria Domínguez

Centro de Investigación en Ciencias Medicas, Jesús Carranza No. 200 esq. Venustiano Carranza, Col. Universidad. Toluca, Estado de México, México. CP 50130. Tel: +52 (722) 219-41-22 and 212-80-27 ext.114.

Cell phone: +521(722)393-42-27. E-mail: mavidoga@yahoo.com.mx

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Abstract

Background. Occult chronic kidney disease (OCKD) and cardiovascular risk (CVR) share risk factors that trigger chronic degenerative diseases. Aim. To assess the association of OCKD with CVR and its risk factors in a sample of university workers. Material and methods. This is a cross-sectional study. From 89 volunteers the lipid profile, glucose, urea, creatinine and uric acid were obtained from blood as well as anthropometric measures and blood pressure. They were classified by their CVR calculated by the Framingham equation, into the groups: with-CVR and without-CVR; and by their glomerular filtration rate (GFR) into: with-OCKD and without-OCKD. Then into sub-groups of each CVR factor (CVRF): sex, smoking, diabetes mellitus (DM) and hypertension. The statistical differences between groups ($p < 0.05$) and the correlation between CVR and GFR and the odds ratio (OR) for each CVRF were determined. Results. A negative correlation between the OCKD and the CVR was obtained for men ($\rho = -0.743$, $p = 0.000$) and women ($\rho = -0.874$, $p = 0.000$). The overall prevalence of hypertension was 23.6% (OR = 15.43 for CVR, 95% CI, 4.04 - 58.95, OR = 14.75 for OCKD, 95% CI 2.76 - 78.23) and older than 50 years of 33.7% (OR for CVR = 20.37, 95% CI, 6.25 - 66.43). Conclusions. OCKD is strongly associated with the CVR. Furthermore, each CVRF impacts in different range and level to the development of cardiovascular disease and kidney failure.

Keywords. Occult chronic kidney disease, cardiovascular risk, glomerular filtration rate, hypertension, diabetes mellitus.

Introduction

In Mexico among the most frequent causes of death in people at productive and at post-productive age are cardiovascular (CVD) and related diseases such as diabetes mellitus (DM), hypertension and ischemic heart disease¹⁻³.

It is widely known that classical cardiovascular risk factors (CVRF), such as smoking, hypertension, DM and elevated non-HDL cholesterol, produce structural and functional changes in the endothelium, causing its chronic inflammation and its dysfunction, characterized by reduced bioavailability of the vasodilator nitric oxide (NO). These factors generate a vasculature highly susceptible to rupture of the atherosclerotic plaque and thus significantly elevate the cardiovascular risk (CVR)⁴.

The occult chronic kidney disease (OCKD), which involves a decrease in the glomerular filtration rate (GFR), is a major public health problem that recently has increased its incidence. Since the OCKD comes along with a high CVR, it is important in the clinical practice to evaluate both in order to establish the best treatment⁵. There are several equations for measuring GFR; one of these is the Jelliffes equation, which considers serum creatinine, sex and age as the most important variables⁶.

Tobacco smoking alters the hemodynamic balance, affecting blood pressure, cholesterol levels, oxygen transport and homeostasis in the systems of coagulation and inflammation. Because of this, it is attributed that 25-30% of tobacco deaths are due to CVD⁷⁻¹⁰, there is also evi-

dence that women smokers who take oral contraceptives increase their RCV and they tend to have an early onset of menopause. Quitting smoking reduces this risk and improves the prognosis of CVD regardless of the duration of the habit¹¹.

Hypertension is a major public health problem and its etiology, diagnosis and control are not yet well understood. It is associated with multiple risk factors such as obesity, dyslipidemia, hypernatremia and insulin resistance. It is known that the rise in the production of reactive oxygen species oxidize the endothelial NO, but it can also be caused by hyperinsulinemia, as insulin also acts as a vasodilator and therefore in a state of insulin resistance, the vasoconstrictor endothelin-1 is produced and consequently this generates endothelial dysfunction^{12,13}.

Hyperglycemia in DM is the cause of the microangiopathic complications, increasing the production of reactive oxygen species and inflammatory intermediates. It also interferes with insulin signaling and promotes endothelial dysregulation^{4,12}.

Cholesterol is an important structural component of cell membranes, hormones and bile acids and it is transported in the blood attached to lipoproteins. Elevated levels of low density (LDL) lipoproteins and low levels of high-density (HDL) are associated with CVD, because of the highly atherogenic and oxidizable nature of LDL¹⁴. Moreover it has been demonstrated that alone low levels of HDL are predictors of CVD¹⁵.

Since OCKD and CVD share most risk factors, it is important to find the relationship between the pathological processes of the CVRF towards the development of CVD and OCKD. Thus, the aim of this study was to assess the association of occult chronic kidney disease (OCKD) with cardiovascular risk (CVR) and its risk factors (CVRF) in a sample of university workers.

Population

This was a cross-sectional study. 200 workers from the Autonomous University of the State of Mexico of the city of Toluca were invited to participate. Their selection was according to their CRF: age, sex, hypertension, tobacco smoking and DM. None of the volunteers had any cardiac, hepatic nor renal condition, cancer, autoimmune diseases, infectious processes, pregnancy nor was taking anti-inflammatory drugs, antihistamic, or lipid-lowering medication on a regular basis. The research protocol met the ethical standards of the Declaration of Helsinki and was approved by the Ethics and Research Committee of the Medical Sciences and Research Center. The 114 volunteers who agreed to participate gave their informed consent and a validated questionnaire about lifestyle and health conditions¹⁶.

Blood sample collection

Blood samples were collected after a fasting period of 12 hr. Glucose levels were measured by the glucose hexoki-

nase method (Randox). Urea, creatinine, and uric acid, were assayed with colorimetric methods (Randox). For the lipid profile, triglycerides (TG) were determined by their enzymatic hydrolysis and then followed by a colorimetric reaction, HDL and LDL lipoproteins were measured using a clearance method and total cholesterol (TC) with an enzymatic colorimetric method (Randox)^{16,17}.

Study Groups

Using the information obtained from questionnaires, the results of anthropometric measurements and the blood tests; volunteers were grouped as follows:

Cardiovascular risk. The percentage of RCV was calculated using with the Framingham equation up to ten years^{18,19} and validated for Hispanics²⁰. The cutoff points used were $\leq 10\%$ for group without cardiovascular risk (without-CVR) and $>10\%$ for the group with cardiovascular risk (with-CVR)²¹⁻²³. Smokers and diabetics were excluded from the group without-CVR to avoid interference of these factors on the results.

Subgroups

Occult chronic kidney disease. It was calculated with the formula for the glomerular filtration rate of Jelliffes⁶, taking $<60\text{mL}/\text{min}/1.73\text{m}^2$ as the cutoff for OCKD.

Age. The selected cutoff was of 50 years old or more.

Tobacco smoking. Were considered smokers those volunteers who smoked at least one cigarette a week or more than four per month.

Diabetes mellitus. Volunteers classified as diabetics were those who reported it in the questionnaire or those that glucose measurements in their blood sample exceeded 120 mg/dL.

Hypertension. Blood pressure was measured by a sphygmomanometer. Three measurements were taken and the average of the last two was reported. An optimal-normal pressure was considered as systolic <129 mm Hg or diastolic <84 mm Hg and for hypertension was systolic ≥ 130 mm Hg or diastolic ≥ 85 . When the systolic or diastolic pressure fell into different categories, the highest category was selected for classification. It was not considered the intake of antihypertensive drugs.

Overweight and obesity. The body mass index (BMI) was calculated. The weight was measured using a body composition analyzer (Tanita), and height with a conventional stadiometer. BMI over 26 was considered overweight-obesity.

Menopause-postmenopause. Female volunteers that in the questionnaire reported this.

Statistical analysis

Microsoft Office Excel 2007 was used to calculate the RCV of the Framingham equation. The questionnaire data and blood tests results were analyzed using the statistical package PAWS Statistics version 18.0. Descriptive statistics were obtained for all continuous variables. The distribu-

tion of data was assessed using the Shapiro-Wilk test for normality and the Levene test for homogeneity both with a significance of $p \leq 0.05$, depending on the results it was determined the proper statistical comparison test (Student t test for parametric data and test Mann-Whitney test for nonparametric data) between groups of RCV and OCKD. The association between the RCV and OCKD was tested with the Spearman correlation coefficient between the Framingham and Jelliffes equations. We calculated the odds ratio (OR) of each subgroup towards the development of a high CVR and OCKD.

Results

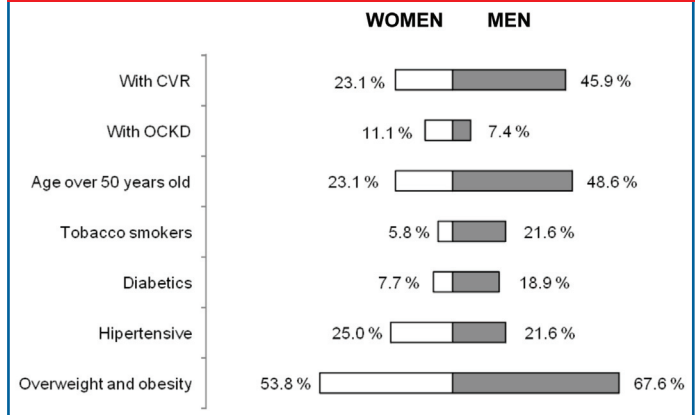
The number of volunteers who met the inclusion criteria was 89 individuals, 52 women (42.73 ± 9.7 years) and 37 men (50.65 ± 10.3 years). It was observed (Table 1) that in men the average levels of CT are about 8 units above the recommended levels (200 mg/dL) and that there is a wide dispersion of its values in both sexes. LDL averages are above the standard parameters (up to 130 mg/dL) and HDL are below recommended values (>55 mg/dL in men and >65 mg/dL in women).

Table 1. Blood test results of volunteers (women: n=52; men: n=37).

Parameter	Sex	Mean \pm SD
Glucose (mg/dL)	Women	91.46 \pm 15.43
	Men	107.41 \pm 36.20
Urea (mg/dL)	Women	24.35 \pm 5.96
	Men	30.71 \pm 5.26
Creatinine (mg/dL)	Women	0.92 \pm 0.88
	Men	1.10 \pm 0.20
Uric acid (mg/dL)	Women	3.38 \pm 0.83
	Men	5.29 \pm 1.20
TG (mg/dL)	Women	136.60 \pm 77.11
	Men	180.68 \pm 93.07
CT (mg/dL)	Women	190.31 \pm 42.62
	Men	207.70 \pm 33.02
HDL (mg/dL)	Women	44.31 \pm 10.23
	Men	41.46 \pm 8.99
LDL (mg/dL)	Women	97.90 \pm 28.07
	Men	109.62 \pm 21.88

45.9% of men and 23.1% of women belonged to the with-CVR group ($>10\%$ of score Framingham), while the incidence of OCKD in men was 7.4% and 11.1% in women (Figure 1).

Figure 1. Classification of volunteers by cardiovascular risk and cardiovascular risk factors (women: n=52; men: n=37).



The correlation analysis (Figures 2 and 3) indicated a strong negative relationship between the Jelliffes equation for calculating the GFR and Framingham equation for CVR for both women ($\rho = -0.874$, $p = 0.000$) and men ($\rho = -0.743$, $p = 0.000$).

Figure 2. Bivariate correlation analysis between Framingham and Jelliffes equation for women.

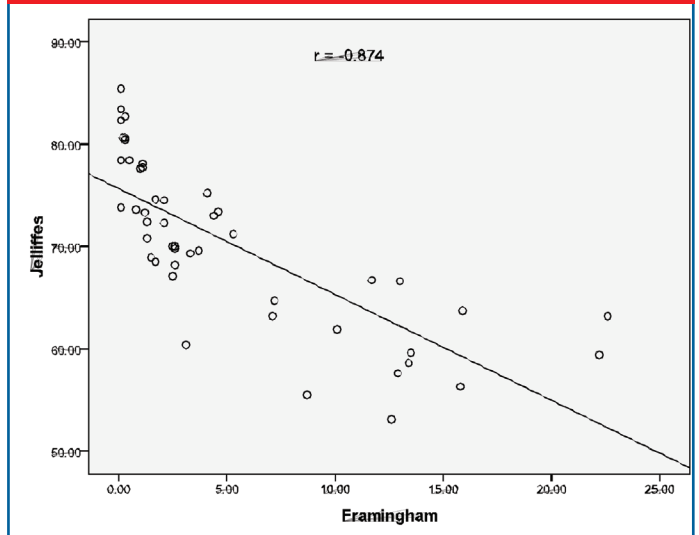
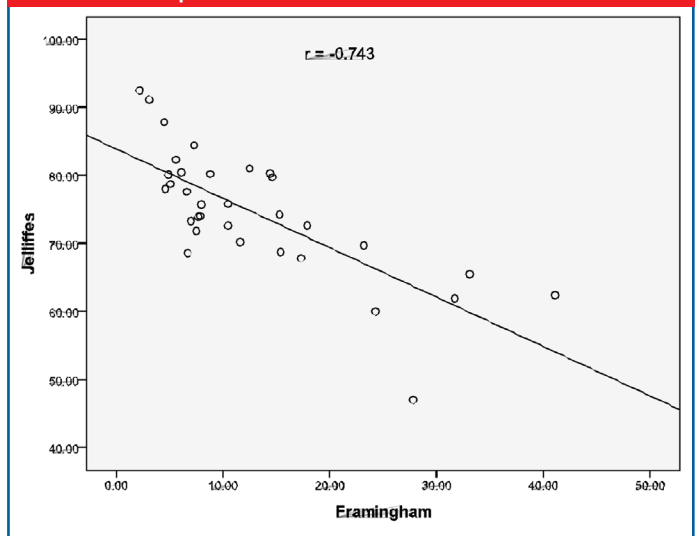


Figure 3. Bivariate correlation analysis between Framingham and Jelliffes equation for men.



The comparison of the continuous variables between groups indicated significant differences in CVR for men when considering the age. In women differences were found in age, levels of glucose and TG, TC and LDL. In the OCKD groups differences for men and women were found in age, and in women only with elevated glucose and creatinine decreased (Table 2).

OR analysis between groups of CVR indicated that each of the factors impacted with a different magnitude, greatly

increasing the CVR the age over 50 years and hypertension. It was found that men had a higher CVR and also for them the factor with a greater impact is age, followed by hypertension, tobacco smoking, and finally DM. In women was found that menopause-postmenopause, hypertension and DM are the factors that by far increase CVR. The results pointed that hypertension was the factor with the greatest impact towards the development of OCKD (Table 3).

Table 2. Descriptive statistics of continuous variables by groups of CVR and OCKD for men and women.

Parameter	Sex	With-CVR	Without-CVR	p≤0.05	With-OCKD	Without-OCKD	p≤0.05
		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age (years)	Women	54.42 ± 3.75	39.23 ± 8.03	0.000 ^{1*}	57.29 ± 3.09	40.29 ± 8.48	0.000 ^{1*}
	Men	57.06 ± 8.76	45.2 ± 8.15	0.000 ^{1*}	73.00 ± 7.07	49.75 ± 8.94	0.001 ^{1*}
Glucose (mg/dL)	Women	104.08 ± 24.16	87.68 ± 9.12	0.004 ^{2*}	110.00 ± 28.86	88.29 ± 10.34	0.001 ^{1*}
	Men	119.47 ± 49.83	97.15 ± 12.27	0.390 ²	110.50 ± 30.41	107.38 ± 37.95	0.910 ¹
Urea (mg/dL)	Women	25.63 ± 6.22	23.97 ± 25.91	0.422 ¹	26.14 ± 6.57	24.05 ± 5.88	0.396 ¹
	Men	31.50 ± 5.79	30.00 ± 4.80	0.415 ¹	31.50 ± 6.36	30.66 ± 5.30	0.830 ¹
Creatinine (mg/dL)	Women	0.92 ± 0.08	0.92 ± 0.09	0.942 ¹	0.87 ± 0.06	0.93 ± 0.09	0.088 ^{1*}
	Men	1.06 ± 0.11	1.14 ± 0.26	0.225 ¹	0.96 ± 0.07	1.11 ± 0.20	0.089 ²
Uric acid (mg/dL)	Women	3.79 ± 0.97	3.25 ± 0.76	0.062 ¹	3.56 ± 0.86	3.34 ± 0.83	0.524 ¹
	Men	5.11 ± 1.48	5.46 ± 0.92	0.424 ¹	4.02 ± 1.20	5.37 ± 1.18	0.128 ¹
TG (mg/dL)	Women	189.00 ± 101.32	120.88 ± 61.50	0.011 ^{2*}	167.71 ± 86.26	132.98 ± 78.17	0.290 ¹
	Men	188.00 ± 90.64	174.45 ± 96.99	0.752 ²	181.00 ± 100.41	180.38 ± 96.39	0.993 ¹
CT (mg/dL)	Women	217.42 ± 53.66	182.18 ± 35.62	0.013 ^{2*}	193.29 ± 29.50	187.98 ± 44.90	0.765 ¹
	Men	216.94 ± 33.23	199.85 ± 31.53	0.118 ¹	197.50 ± 4.95	208.16 ± 34.14	0.667 ¹
HDL (mg/dL)	Women	41.17 ± 7.76	45.25 ± 10.76	0.229 ¹	43.86 ± 5.84	42.83 ± 8.95	0.772 ¹
	Men	41.76 ± 8.02	41.2 ± 9.93	0.852 ¹	40.00 ± 4.24	40.59 ± 8.89	0.927 ¹
LDL (mg/dL)	Women	114.5 ± 37.16	92.93 ± 23.04	0.041 ^{2*}	96.00 ± 19.01	96.93 ± 29.59	0.937 ¹
	Men	115.47 ± 22.2	104.65 ± 20.86	0.136 ¹	104.00 ± 8.49	109.31 ± 22.27	0.742 ¹

(*) Statistically significant; (1) T-Student test; (2) U Mann-Whitney test

Table 3. OR of classical risk factors towards the development of cardiovascular disease and occult chronic kidney disease.

Group	Variable	OR for CVR (95% CI)	OR for OCKD (95% CI)
Total simple	Age over 50 years old	20.37 (6.25 – 66.43)	SNS
	Hipertension	15.43 (4.04 – 58.95)	14.75 (2.76 – 78.23)
	Male sex	2.83 (1.14 – 7.10)	SNS
Men	Age over 50 years old	9.75 (2.15 – 44.14)	SNS
	Hipertension	1.89 (1.21 – 2.96)	SNS
	Tobacco smoking	1.89 (1.21 – 2.96)	SNS
	Diabetes mellitus	1.70 (1.41 – 2.53)	SNS
Women	Menopause-postmenopause	9.00 (2.03 – 39.93)	12.92 (1.41 – 118.61)
	Hipertension	7.94 (1.88 – 33.45)	29.14 (3.02 – 281.5)
	Diabetes mellitus	1.50 (1.01 – 2.24)	16.00 (1.22 – 209.93)

SNS: statistically not significant

In a population that reflects a sector of society with a moderate standard of living and income, such as university workers, a high prevalence of hypertension was observed, as well as high prevalence of obesity, overweight, and smoking that are CVD preventable factors. So the wide dispersion of these parameters is attributed to the large interindividual variability. Nonetheless, the Framingham equation allowed to properly classify the volunteers according to their CVR, showing that it is appropriate to use it in the Mexican population. Due to the low number of participants, diabetics and smokers were excluded from the group without-CVR to avoid losing significance in the subsequent analysis. However, it should be noted that these had low percentage of risk due mainly to its relatively young age.

It is alarming to note that men have high cholesterol levels regardless of the level of CVR, indicating a propensity to develop atherosclerotic plaques, which increases with age, similar to what the Framingham equation poses.

The high incidence of overweight and obesity combined with elevated cholesterol levels indicates a high probability of developing CVD, especially with aging and the incidence of other CVRF as smoking, hypertension, diabetes mellitus and a diet high in fat and low in fiber and antioxidants. Due to the presence of receptors, the adipose tissue responds to physiological and metabolic processes of various organs including the CNS by modulating the secretion of adipocytokines such as adiponectin, which has antiatherogenic, anti-inflammatory, and antidiabetic properties. This cytokine improves insulin sensitivity and activates the NO synthesis which protects the vasculature. The CVRF decrease the adiponectin levels, promoting a proinflammatory state and the development of related pathologies²³⁻²⁶.

The bivariate correlation analysis showed that a decrease in the GFR and increased CVR are closely linked, so it is assumed that both share risk factors and surely some metabolic pathways. Similar findings were observed in the study of Buitrago F. et al. OCKD was present in high CVR people calculated from the Framingham equation, and moreover it was associated with high BMI and older age²⁷.

This study shows that age, hypertension, and to a lesser extent DM and smoking were the factors that influenced more on the classification of people with CVR. These factors impact in different sizes and at different levels to the development of CVR between both sexes. Men had a risk approximately 3 times higher than women to develop high CVR and for men older than 50 years the risk increased about 10 times and nearly double in those who had hypertension, DM or smoking habits. These are lower values than those reported by Tartaglione et al. For adult men with hypertension (OR = 2.3, 95% CI, 1.3-3.9), DM

(OR = 4.5, 95% CI, 2.1-9.8) and smoking (OR = 1.48, 95% CI, 0.97-2.28) [28]. In contrast, women showed an increased risk of CVD after menopause and in those who had hypertension and DM.

Menopausal women who have an increased CVR suffer heart attacks more severe than men. After a heart attack, the chance of dying within a year increases by 50% compared to men and the risk of a second attack is two times higher in the next six years²⁹. This is due to a depressed estrogen synthesis. It is well known that estrogens play a protective role by participating in the metabolism of lipoproteins (diminish LDL and raise HDL and apolipoprotein A1), in the process of hemostasis (modulate the release of prostacyclin, NO, endothelin, thrombomodulin and heparan sulfate in the endothelium), and in the responses of smooth muscle cells towards the blood pressure (avoid contraction by inhibition of K⁺ channels and Ca²⁺ L-type) [30].

It can be deduced from the pathological process of CVD and OCKD that the risk factors are involved not only into the frequency and severity in which they affect the individual health, but also they are key factors for the prevention, mainly those with greater impact as hypertension, so preventing and controlling this risk factor, it is possible to prevent both conditions: CVD and OCKD. On the other hand, it is not possible to take control of non-modifiable factors (sex, age, DM), but it is possible to take preventive measures to compensate the endothelial damage, especially involving the smoking habits, a sedentary lifestyle and an unbalanced diet.

It is relevant to point out that subjects with CVR should consider the physician recommendations according to age, family history and underlying diseases of each person.

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