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High Levels of hsCRP are Associated With Carbohydrate Metabolism Disorder

Elba Leiva,[1] Verónica Mujica,[1] Katherine Brito,[1] Ivan Palomo,[2] Roxana Orrego,[1] Rodrigo Moore-Carrasco,[1] Marcela Vásquez,[1]* Luis Guzmán,[1] Sergio Nuñez,[1] Nora Díaz,[3] Gloria Icaza,[3] and Miguel Arredondo[4]

[1]*Programa de Investigación de Factores de Riesgo de Enfermedades, Cardiovasculares, Universidad de Talca, Talca, Chile*

[2]*Faculty of Health Sciences, Department of Clinical Biochemistry and Immunohematology, Universidad de Talca, Talca, Chile*

[3]*Instituto de Matemáticas y Física, Universidad de Talca, Talca, Chile*

[4]*Instituto de Nutrición y Tecnología de los Alimentos, Universidad de Chile, Santiago, Chile*

Aim: To determine risk parameters associated with high values of high sensitive C-reactive protein (hsCRP) in subjects with different glucose fasting levels. *Methods*: Anthropometric parameters, arterial pressure, glycemia, lipid profile, uric acid, and hsCRP were studied in a population of 513 individuals between 40 and 65 years. *Results*: In total, 349 (68.0%) were normoglycemic (NG); 113 (22.0%) had impaired fasting glucose (IFG); and 51 (9.9%) were diabetic subjects. A multivariate linear regression analysis showed that the natural logarithm of hsCRP was associated significantly with glycemia levels ($P = 0.009$), uric acid ($P = 0.001$), diastolic blood pressure ($P = 0.011$), smoking habit ($P = 0.021$), BMI ($P < 0.001$), and sex ($P < 0.001$). One-third of the NG subjects had high hsCRP levels. A multiple logistic regression analysis showed that sex and BMI were variables related to high levels of hsCRP in subjects with IFG and NG. In NG subjects, uric acid levels were associated with risk of presenting high hsCRP levels and were higher in women than men. In NG women, ROC curves analysis identified a uric acid level of 3.9 mg/dl as a cut-off point to predict a high value of hsCRP. Those individuals with uric acid values higher than 3.9 mg/dl and normal glycemia had 3.5-fold more risk of having hsCRP levels over 3.0 mg/l. *Conclusions*: We sustain that high levels of hsCRP are associated with disturbance in carbohydrate metabolism. In addition, we believe that in low cardiovascular risk population, such as NG women, uric acid levels above 3.9 mg/dl might represent a signal of possible pro-inflammatory state and cardiovascular risk. J. Clin. Lab. Anal. 25:375–381, 2011.

Key words: impaired glucose; uric acid; cardiovascular diseases; diabetic

INTRODUCTION

It is well known that acute hyperglycemia can exert deleterious effects on the arterial wall through mechanisms including oxidative stress, endothelial dysfunction, and activation of the coagulation cascade and long-term hyperglycemia causes diabetes-specific microvascular complication (retinopathy, nephropathy, and neuropathy). In addition, patients with uncontrolled diabetes mellitus sometimes suffer also athero-thrombotic disorders, such as coronary or cerebrovascular obstruction, which may occur or begin with mild or even postprandial hyperglycemia (1,2).

Data clearly show that the constellation of risk factors such as hyperglycemia, hyperinsulinemia, and high plasma cytokine levels produces an increased risk of cardiovascular events in rats (3) and in humans (4). Capuzzi and Freeman (5) had hypothesized a strong

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*Correspondence to: Marcela Vásquez, Programa de Investigación de Factores de Riesgo de Enfermedades, Cardiovasculares, Universidad de Talca, Talca, Chile. E-mail: mvasquro@utalca.cl

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relation between the metabolic disturbances of insulin-resistance; type 2 diabetic patients and the development and progress of atherosclerosis, where pro-inflammatory cytokines such as interleukine-1 and 6, as well as C-reactive protein (CRP) are very important.

CRP is a 115 kDa pentamer synthesized mainly by hepatocytes and adipocytes, under the control of interleukin-6 in the setting of the innate, nonspecific immune response. The gene that codes for CRP is located in chromosome 1 and in humans it is non-glycosylated protein that belongs to the pentraxine family that includes the serum amyloid P (6,7). CRP participates in response to tissular injury and infectious processes. High levels of CRP are related to cardiovascular disease associated with high blood pressure, the maintenance of inflammatory processes, and other characteristics that worsen these diseases (8–10).

The association between elevated CRP levels and high blood pressure may have three different pathophysiological explanations: (1) CRP may induce a decrease in endothelium-dependent relaxation, a potential risk factor for hypertension, (2) CRP may induce inflammation, and (3) on the other hand, the association could be erroneously concluded due to the fact that CRP and high blood pressure share several risk factors such as lower socio-demographic position, lack of physical activity, smoking, and abdominal obesity (11).

Many studies have shown that CRP have proinflammatory and proatherogenic characteristics for diminishing nitric-oxide and prostacycline synthesis in endothelial cells and raising levels of: endothelin I, adhesion molecules, monocyte chemoatractant protein I, interleukin-8, and PAI-I in macrophages, besides inducing the tissue factor secretion participating in chemotaxis, raising the reactive oxygen species (ROS) and LDL oxidation (12,13).

Iwasaki et al. (14) published the effect of high glucose on nuclear factor kappa-B-dependent transcription in human hepatocyte cell line in vitro, suggesting that glucose per se would be responsible for activating the protein expression related with inflammation and coagulation by increasing the oxidative stress. In acute phase response this protein would be beneficial, but the over expression is responsible for the hypercoagulability state that leads to thrombotic and atherosclerotic disorders (15).

Moreover, it has been proposed that CRP could be used for predicting cardiovascular disease risk in metabolic syndrome subjects (adjusted by age, sex, and ethnicity) (16,17). Also, a relationship has been found between plasmatic concentration of CRP and cardiovascular risk, obtaining that plasmatic concentration lower than 1.0 mg/l was considered low risk, between 1 and 3 mg/l intermediate risk, and higher than 3.0 mg/l was considered high risk for cardiovascular disease (18,19).

Previous results of our Research Program of Risk Factors for Cardiovascular Disease at Talca University, on a random sample of individuals between 18 and 74 years of age in Talca, Chile, showed that 26.3% present IFG and 6.1% are in treatment for diabetes, 70.1% of them are obese or overweight, 36.7% have high blood pressure, and 44.5% suffer from hypercholesterolemia (20). Our aims was to contribute to the identification of populations at the greatest risk of developing both diabetes and cardiovascular disease.

PATIENTS AND METHODS

Study Population

A total of 513 adult subjects, 157 (30.6%) men and 356 (69.4%) women, between 40 and 65 years old, were selected from 1,007 individuals from the Research Program study in Talca, Chile. Weight, height, waist perimeter, and blood arterial pressure were measured according to the NIH recommendations (21,22) and venous blood samples were collected from patients after 12 hr overnight fasting to determine glycemia, lipid profile, and uric acid levels (all of them Roche Laboratories, Mannheim, Germany) in a HITACHI 717 auto-analyzer. High sensitive C-reactive protein (hsCRP) was measured by immunoturbidimetry method. As an internal standard we used the reference CRM 470 and RPPHS (Referent Preparation for Proteins in Human Serum) and for quality control CRPT control N, Ref 20766321 (USA 0766321).

Population Classification

According to American Diabetes Association (ADA) criteria (23), subjects were classified in three groups of glycemia levels: (a) normoglycemic (NG) when glycemia level was <100 mg/dl; (b) impaired fasting glucose (IFG) when glycemia level was found between 100 and 126 mg/dl, and (c) diabetic when glycemia level was >126 mg/dl and or when they were being treated with hypoglycemic drugs. Also, the subjects were classified in two categories according theirs hsCRP levels: (1) hsCRP <3 mg/l and (2) hsCRP >3 mg/l.

Statistical Analysis

The distributions of the studied variables were not normal, therefore they are described through the median and inter-quartile range (75th−25th percentile). Non-parametric Mann–Whitney U test was used to compare each variable by sex. To identify which cardiovascular risk factors (glucose levels, blood pressure, waist circumference, total cholesterol, LDL cholesterol,

TABLE 1. Anthropometric and Biochemical Description of the Subjects

	Men $n = 157$ Median (QIR)	Women $n = 356$ Median (QIR)	Total $n = 513$ Median (QIR)	P-value*
Age (years)	50.0 (12.5)	50.0 (11.5)	50.0 (11.0)	0.42*
Weight (Kg)	80.8 (19.1)	69.0 (18.0)	73.1 (18.6)	< **0.001***
Height (mt)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)	< **0.001***
BMI (Kg/mt^2)	28.3 (4.7)	28.3 (7.6)	28.3 (6.3)	0.46*
Waist (cm)	98.0 (13.0)	90.0 (18.0)	93.0 (17.0)	< **0.001***
Glycemia (mg/dl)	96.0 (16.0)	92.0 (18.0)	93.0 (17.0)	<**0.001***
hsCRP (mg/l)	1.5 (2.4)	2.5 (4.3)	2.2 (3.6)	<**0.001***
Uric acid (mg/dl)	5.7 (1.7)	4.2 (1.5)	4.5 (1.7)	<**0.001***
Total cholesterol (mg/dl)	196.0 (50.0)	206.0 (50.0)	203.0 (52.0)	**0.02***
LDL cholesterol (*)[a]	116.0 (38.0)	120.0 (42.0)	118.0 (42.0)	0.26*
HDL cholesterol (mg/dl)	43.0 (15.5)	52.0 (20.0)	49.0 (19.0)	< **0.001***
Triglycerides (mg/dl)	165.0 (136.0)	140.0 (94.5)	146.0 (100.0)	< **0.001***
Systolic pressure (mmHg)	132.0 (26.5)	125.0 (23.5)	126.5 (24.5)	< **0.001***
Diastolic pressure (mmHg)	81.5 (16.3)	77.5 (15.4)	78.0 (15.3)	< **0.001***
Smoking (n, %)	57 (36.3)	120 (33.7)	177 (34.5)	0.57**

Median and (interquartile ranges) were used. BMI: Body mass index; hsCRP: highly sensitive C-reactive protein.
[a]$n = 492$.
*Mann–Whitney U test.
**Chi-square test.

HDL cholesterol, triglycerides, uric acid, and smoking) are related to hsCRP levels, a multivariate regression analysis was realized, adjusting by age and sex. As hsCRP was not normally distributed, the natural logarithm transformation was used. To identify which risk factors are related to high hsCRP levels (>3 mg/l), among NG and IFG subjects, a multivariate logistic regression analysis was performed, adjusting by age and sex. The diabetic subjects were not included because they have other additional risk factors of cardiovascular disease. ROC curve analysis was used to determine uric acid cut-off points to predict high hsCRP levels (>3 mg/l) in women and men with normal glucose levels.

RESULTS

In this study we examined 513 individuals, 157 men (30.6%) and 356 women (69.4%). Theirs general characteristics are presented in Table 1. The majority of the population had overweight and had high total cholesterol levels. This confirms the high prevalence of cardiovascular risk factors in apparently healthy people.

We found 349 (68.03%) NG individuals, 113 (22.03%) with IFG, and 51 (9.9%) diabetic subjects. The median value of hsCRP level in NG men was 1.1(RI 1.8) mg/l, in IFG 2.1 (RI 3.1) mg/l, and in diabetic 2.7 (RI 3.0) mg/l. In NG women, hsCRP median value was 2.1 (RI 3.7) mg/l, in IFG 3.3 (RI 5.0) mg/l, and in diabetic 4.0 (5.3) mg/l (Table 2). These results showed that women had significantly higher levels of hsCRP than men and both present a median of 2.2 mg/l which suggests an intermediate cardiovascular risk.

Multivariate linear regression showed that glucose levels ($P = 0.009$), uric acid ($P = 0.001$), diastolic blood pressure ($P = 0.011$), smoking habit ($P = 0.021$), BMI ($P < 0.001$), and sex ($P < 0.001$) were variables related to the natural logarithm (ln) of hsCRP. Considering this model, we can deduce that for each glucose increase unit, there is a significant raise of ln hsCRP levels (R^2: 20.1%). The positive relationship between the adjusted ln hsCRP values in women and men and glucose levels are shown in Figure 1. Among NG subjects, 117/349 had hsCRP levels >3 mg/l (17.1% men and 82.9% women) (Table 2).

Logistic regression in people with IFG showed that sex and BMI were significant variables that determine a high level of hsCRP. However, the same analysis in NG subjects found that besides the BMI and sex, uric acid was a significant variable to explain high levels of hsCRP (Table 3). We found that for each increase unit on BMI (k/m^2) the risk to have high hsCRP levels raises in 10.9% (95% CI: 1.05–1.17) and for each mg/dl increase of uric acid, the risk to have high hsCRP raises 28.0% (95% CI: 1.01–1.62). Additionally, we found that the risk was 3.5 times higher in women than in men (95% CI: 1.70–7.20). Therefore, uric acid could be a discriminant variable between having high or low hsCRP levels in individuals with normal glycemia. The relationship between uric acid levels and the probability of having high levels of hsCRP for NG and IFG subject is shown in Figure 2. An increased level of uric acid produces an increased risk of high hsCRP levels only in NG subjects.

TABLE 2. Anthropometric and Biochemical Description of the Subjects

	Men $n = 157$				Women $n = 356$			
	Glycemia <100 mg/dl $n = 97$	Glycemia 100–126 mg/dl $n = 40$	Glycemia ≥ 126 mg/dl $n = 20$	P	Glycemia <100 mg/dl $n = 252$	Glycemia 100–126 mg/dl $n = 73$	Glycemia ≥ 126 mg/dl $n = 31$	P
Age (years)	49.0 (13.0)	54.5 (11.8)	54.0 (8,8)	**0.017***	49.0 (10.0)	53.0 (11.0)	54.0 (15.0)	**<0.001***
Weight (Kg)	79.0 (16.4)	86.4 (18.8)	90.8 (14.6)	**<0.001***	66.5 (17.0)	77.9 (16.1)	76.2 (15.4)	**<0.001***
Height (mt)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	0.983*	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	0.763*
BMI (Kg/mt^2)	27.5 (4.7)	29.7 (4.5)	30.5 (6.3)	**<0.001***	27.4 (6.8)	31.6 (7.4)	32.0 (8.4)	**<0.001***
Waist (cm)	95.0 (10.0)	100.0 (17.8)	104.0 (12.8)	**<0.001***	88.0 (15.8)	97.0 (17.0)	98.0 (16.0)	**<0.001***
Glycemia (mg/dl)	90.0 (9.0)	105.0 (10.0)	176.5 (85.3)	**<0.001***	87.0 (12.0)	106.0 (8.5)	139.0 (80.0)	**<0.001***
hsCRP (mg/dl)	1.1 (1.8)	2.1 (3.1)	2.7 (3.0)	**0.001***	2.1 (3.7)	3.3 (5.0)	4.0 (5.3)	**<0.001***
Uric acid (mg/dl)	5.5 (1.5)	5.8 (1.3)	6.2 (2.7)	0.497*	4.0 (1.3)	4.6 (1.6)	4.5 (2.0)	**<0.001***
Total cholesterol (mg/dl)	199.0 (48.5)	193.0 (57.3)	191.5 (66.0)	0.945*	205.5 (50.0)	205.0 (47.5)	212.0 (59.0)	0.626*
LDL cholesterol[a] (mg/dl)	120.0 (43.0)	113.0 (45.0)	110.0 (16.5)	0.600*	118.0 (41.0)	122.0 (39.0)	126.0 (49.5)	0.707*
HDL cholesterol (mg/dl)	43.0 (17.5)	43.0 (12.0)	39.5 (13.8)	0.351*	54.0 (22.8)	47.0 (13.5)	43.0 (15.0)	**0.001***
Triglycerides (mg/dl)	164.0 (134.0)	164.0 (84.8)	210.5 (510.0)	0.14*	137.5 (85.8)	139.0 (94.5)	204.0 (117.0)	**<0.001***
Systolic pressure (mmHg)	126.5 (25.3)	135.3 (28.6)	144.0 (18.3)	**<0.001***	122.5 (24.4)	134.0 (19.5)	128.0 (17.5)	**<0.001***
Diastolic pressure (mmHg)	78.0 (13.5)	85.5 (12.0)	88.0 (12.8)	**0.002***	76.5 (15.4)	80.5 (13.3)	78.0 (9.0)	**0.013***
Smoking (n, %)	(38, 39.2%)	(12, 30.0%)	(7, 35.0%)	0.592**	(93, 36.9%)	(18, 24.7%)	(9.0, 29.0%)	0.127**

Median and (interquartile ranges) were used. BMI: Body mass index; hsCRP: highly sensitive C-reactive protein.

[a]$n = 492$.

*Mann–Whitney U test.

**Chi-square test.

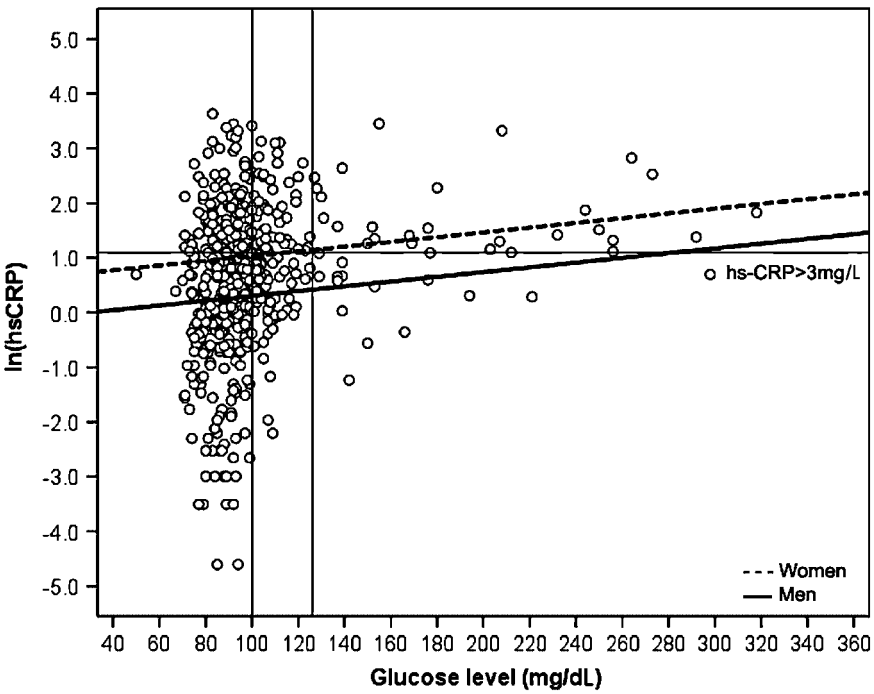

Fig. 1. Relationship between logarithm of hsCRP and glucose levels and adjusted values of multivariate regression model, for men and women.

TABLE 3. Logistic Regression Analysis in Normoglycemic Subjects

Variables	Odds ratio	95% confidence interval for odds ratio	*P*-value
Sex (M vs. F)	3.499	1.701–7.20	0.001
Body Mass Index (BMI)	1.109	1.054–1.167	<0.001
Uric acid	1.280	1.011–1.619	0.040

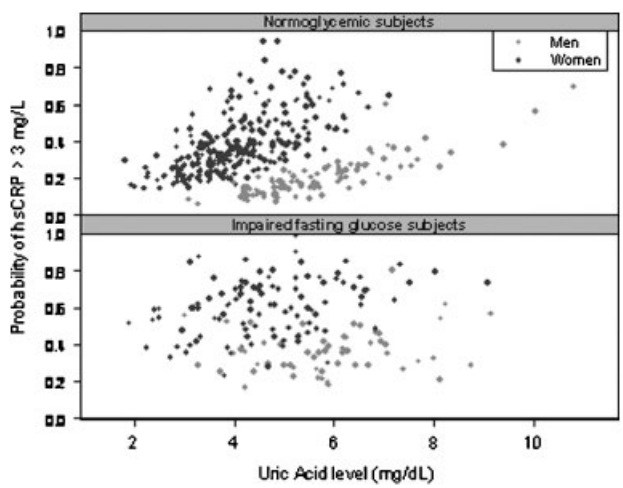

Fig. 2. Relationship between uric acid levels and probability of high levels of hsCRP for normoglycemic and impaired fasting glucose subjects.

ROC curve analysis for NG men showed that the area under the ROC curve was 0.597 (95% CI: 0.493–0.695). However, in NG women this value was 0.645 (95% CI: 0.582–0.704). Therefore, it was possible to identify 3.9 mg/dl as cut-off point of uric acid to predict a high hsCRP value, thus those women with uric acid levels >3.9 mg/dl and normal glycemia have 3.5 times more risk to have hsCRP >3.0 mg/l than women with normal glycemia and uric acid levels ≤ 3.9 mg/dl. This cut-off had a sensibility of 73% and a specificity of 56%.

DISCUSSION

As is widely known, diabetic patients have maximum cardiovascular risk, so it was expected to find the highest frequency of high hsCRP levels among this group. Patients with IFG presented an intermediate frequency and subjects with normal glycemia had the lowest frequency of high hsCRP levels. hsCRP levels had been reported as a predictor of diabetes. Several studies reported a positive association between elevated hsCRP levels and risk of developing diabetes. In our study, 45% of subjects with prediabetes have hsCRP levels higher than 3 mg/l, suggesting that they also have high cardiovascular disease risk. Also, they could have more probabilities of progressing to a state of diabetes. Monica European Study (24) showed that men with hsCRP higher than 3 mg/l had three-fold increased risk of developing diabetes than those in the lowest quartile

adjusted for age. Similar results were reported in the Hisayama Study (25), where the risk of developing diabetes in Japanese subjects was significantly increased in the highest hsCRP quartile. An odds ratio of 2.63 for men and 2.25 for women was reported.

In our studied, 17.1% of men and 82.9% of women with normal glucose values presented hsCRP above 3 mg/l, suggesting that they also could have an increased cardiovascular risk and high possibility of develop diabetes, so we think that it would be interesting to identify a biochemical marker or other factor associated with this risk. In this context, multivariate analysis showed that uric acid levels is an independent factor that seems to be significant to add it to this group with a greatest risk. Uric acid is an old marker whose importance as a cardiovascular risk parameter remains in dispute. Our results support the potential role of uric acid levels as a cardiovascular risk parameter, and it is consistent with Hayden and Tyagi (26) results, who suggested that values of uric acid above 4 mg/dl should be considered a risk factor, which is very similar to our cut-off point of 3.9 mg/dl in NG subjects. Therefore, the uric acid appears as a variable that discriminates between having low or high hsCRP, but only in NG patients, because when blood glucose rises, the discriminatory power of the uric acid is lost.

The relationship between inflammation expressed by increases in hsCRP and hyperglycemia is probably a cause and consequence of insulin resistance, lipo-oxidation, and secretion of acute phase response proteins in adipocytes overloaded fat; together with gluco- and lipo-toxicity, the processes of oxidative stress in pancreatic beta cells contributing to their dysfunction.

Iwasaki et al. (14) demonstrated in liver cells that hyperglycemia per se had a positive effect on the transcription of NF-kB which results in activating the expression of proteins associated with inflammation and clotting through an increase in oxidative stress, even though the mechanisms by which high concentrations of glucose activate NF-kB are not entirely clarified, but the evidence suggests that moderate, but permanent glycosylation generates increased oxidative stress. Schillaci and Pirro (11) argue that CRP can have negative effects on the structure and function of the vascular wall. It had been suggested that not only the liver synthesizes CRP, but also the human atheroma, the smooth muscle cells, and vascular endothelial cells can synthesize CRP.

In summary, we support that high levels of hsCRP are associated with disturbance in carbohydrate metabolism. Besides, we believe that in a low cardiovascular risk group such as NG women, uric acid levels above 3.9 mg/dl might constitute a signal of possible proinflammatory state and cardiovascular risk.

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