Chapter 7

Association Between Creatinine Clearance and Insulin-Resistance in Healthy Adolescent Boys

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1. Introduction

Prevalence of high levels of BMI in both adults and children has been observed in USA [1,2]. Argentina as well, has experienced marked increases in the prevalence of childhood overweight/obesity (OW/OB) over the last few decades [3]. Studies in adults have shown that excess weight is an independent risk factor for end-stage renal disease [4, 5]. Chronic kidney disease is a significant public health problem in the United States, affecting 11% of the U.S. adult population and it has been associated with increased cardiovascular morbidity and mortality [6].

Given the high prevalence and the low awareness of chronic kidney disease, it becomes inevitable to formulate appropriate strategies for the prevention of the chronic kidney disease to control the escalating healthcare cost [7]. A screening program in communities would detect previously unidentified persons at high risk for chronic kidney disease in the general population [8]. OB has been shown to be a strong predictor of chronic kidney disease [4,9,10]. Additionally, studies have suggested an association between insulin resistance and chronic kidney disease [11,12]. A large study performed in a community population in Shanghai, China, showed that OB, hypertension, and anemia, were positively correlated with the development of chronic kidney disease [7].

Few studies have examined the significance of BMI, insulin-resistance and hemoglobin, as risk factors for the development of chronic kidney disease in normal adolescents. The aim of this study was to determine the association between calculated creatinine clearance (CrC) and risk factors for chronic kidney disease such as, BMI, insulin resistance (HOMA-IR), and hemoglobin in healthy adolescents.

2. Methods

2.1. Study design and participants

Data were collected cross-sectionally from 195 adolescent boys aged 16.7 ± 1.8 years, age ranged 15-21 years, in an amateur rugby club in the west side of the Buenos Aires suburbs in April 2009. Exclusion criteria included: missing BMI, blood pressure information, known diabetes or other chronic disease, the use of medication that could alter blood pressure, glucose or lipid metabolism, and the informed consent not being signed. Of the 207 adolescents recruited, 4 were missing the BMI information and 8 declined to participate. The remaining 195 children were included. All subjects were examined by the same physician. The study was approved by the Human Rights Committee of Durand Hospital in Buenos Aires. Each subject and parent gave written informed consent after an explanation of the study and before the initiation of the research studies.

Although Argentina is a Spanish-speaking country, the population differs greatly from what is usually referred to as Hispanic in the U.S. About 85% of the population is of European descent (largely Spanish and Italian), with the remainder of mixed European and American Indian (12%) or American Indian (3%) descent [13]. Socio-demographic characteristics included age, level of education and the presence or absence of a refrigerator and/or a dirt floor. Questionnaires for socio economic status have been described in detail elsewhere [14].

2.2. Anthropometric measures, stage of puberty and blood pressure

Height and weight were measured with subjects wearing light clothing and without shoes. Weight was measured to the nearest 0.1 kg on a medical balance scale. Height was measured to the nearest 0.1 cm. with a wall-mounted stadiometer. Adolescents were classified as normal weight (BMI< 85%), OW (BMI 85% to < 95%), or OB (BMI > or = 95%) according to CDC norms [15]. When participants were older than 18 years they were classified as normal weight (BMI < 25 kg/m^2), OW (25 kg/m^2 ≤ BMI < 30 kg/m^2), or OB (≥30 kg/m^2) according to the adult definition [16]

Waist circumference measurement was taken at the level of the umbilicus and recorded to 0.1cm. A non-elastic flexible tape measure was employed with the subject standing without clothing covering the waist area. Central OB was defined as waist circumference ≥ 94cm per international diabetes federation criteria (IDF) [17].

Three separate blood pressure measurements were recorded by a trained technician using a random-zero sphygmomanometer after the participant was seated at rest for 5 minutes. The averages of the last 3 measurements of systolic and diastolic blood pressures were used [18]. Hypertension was defined according to IDF criteria [17].

Metabolic syndrome was defined according to IDF criteria [17]. Metabolic syndrome is a constellation of metabolic abnormalities that predicts premature coronary artery disease. Recently the IDF [17] developed a simple unified definition for children over 10 years of age. The IDF definition for adolescents included the presence of ≥3 of the following 5 conditions:

[1] central OB (waist circumference >94cm), [2] fasting triglycerides ≥150 mg/dL, [3] HDL-C <40 mg/dL, [4] hypertension with systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥85 mm Hg percentile [5] fasting glucose >100 mg/dL.

The physical examination also included determination of the stage of puberty according to the criteria of Tanner [19].

2.3. Biochemistry

Baseline blood samples were obtained from subjects while they were fasting for 12 hours, for measurement of complete blood count (CBC), levels of glucose, insulin, lipid profile and creatinine. Plasma glucose was obtained by the glucose oxidase technique and serum lipids were measured with a Hitachi Modular P analyser (Hitachi High Technologies Corp., Tokyo, Japan). Serum insulin levels were determined by radioimmunoassay (Diagnostic Products, Los Angeles, CA, USA) and did not cross-react with proinsulin or C-peptide (%CV 5.2-6.8%). Serum creatinine was obtained by the enzymatic method (Bayer, ID-MS, HPLC).

The following equation for HOMA-IR index was used: fasting insulin (uU/l) x fasting glucose (mmol/l)/22.5) [20].

2.4. Estimated glomerular filtration rate

Kidney Disease Improving Global Outcome organization [21] recommended the estimation of glomerular filtration rate, using the simplified equation. Several formulas are widely used in clinical practice: The Schwartz equation is used and validated for adolescents [22]. The abbreviated Modification of Diet in Renal Disease and quadratic equation (MDRD) is used for individuals older than 18 years old [23].The Cockcroft–Gault equation [24] was not used for analysis because it introduces a major methodological problem. Since weight is already included in the numerator of the equation, the association between BMI and CrC would be obvious.

2.5. Data analysis

Chi squared test was used to compare proportions. When more than 20% of the cells had expected frequencies <5, Fisher's exact test was used. The fit to normal distribution of continuous variables was assessed using the Shapiro-Wilks test. When comparing two groups with normally distributed data, a student t test was performed. When comparing more than three groups and with data that were normally distributed, one-way Analysis of Variance was used (Student-Newman-Keuls post hoc test). When the homogeneity of the variances could not be proven, we used the non-parametric Kruskal Wallis instead of Analysis of Variance, with Dunn post hoc test. We evaluated the correlation of plasma CrC with components of the metabolic syndrome using Spearman correlation coefficients. The primary focus of the analysis was to determine the association between calculated CrC and risk factors for chronic kidney disease. Multiple linear regression analysis using CrC as the dependent variable was used. In order to obtain an r squared in each step, a stepwise method was used. P values <0.05 were considered significant in the two-tailed situation. Data are presented as mean ± SD unless otherwise stated.

Analyses were done using the SPSS (Chicago, IL) statistical software package SPSS version 10.0 ®.

3. Results

3.1. Physical and metabolic characteristics:

Participants came from a middle-low socioeconomic class, reflected in their parents' educational background, with 51.8% of mothers and 53.3% of fathers having completed an elementary school education or less. All of the families had a refrigerator and none had a dirt floor. All participants were at pubertal or post pubertal stage. Accordingly, clinical and metabolic characteristics are presented in Table 1.

	Mean	±Std. Deviation
Age (years)	16.73	±1.78
BMI(Kg/m^2)	25.20	±4.99
Waist Circumference (cm)	83.58	±12.95
Systolic BP(mmHg)	115.90	±11.59
Diastolic BP(mmHg)	71.16	±8.56
Hemoglobin (g/dL)	14.76	±0.911
Creatinine (mg/dl)	0.93	±0.17
Cholesterol(mg/dl)	157.13	±33.93
HDL-C(mg/dl)	44.09	±11.77
Insulin(mU/l)	7.69	±5.81
LDL-C(mg/dl)	99.89	±33.06
HOMA-IR	1.61	±1.32
Cr C(ml/min)	128.44	±28.16
OB%	24.1%	(47/195)
OW %	21.0%	(41/195)
Central OB	23.6%	(45/191)
Tanner 3	11.3%	(20/195)
Tanner 4	32.1%	(57/195)
Tanner 5	55.4%	(95/195)

BP, blood pressure. Data are mean ±S.D. or percentage.

Table 1. Clinical and metabolic characteristics

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3.2. Physical and metabolic characteristics according to the presence of OW/OB

Adolescents were divided by the presence of OW/OB. The prevalence of OB adolescents was 47 (24.1%), and of OW 41 (21.0%). There was no significant difference in age between the groups. Clinical and metabolic characteristics according to the presence of OW/ OB are presented in Table 2. Mean values of BMI, triglycerides, systolic blood pressure, diastolic blood pressure, insulin, and HOMA-IR were significantly higher while HDL-C was significantly lower in the group of children with OW or OB (Table 2). Mean values of CrC were not significantly different among normal weight and OW or OB adolescents.

	Normal Weight			OW			OB		
	N=107			N=41			N=47		
Age (c) (years)	16.52	+	1.73	16.45	+	1.81	16.52	+	1.80
BMI(a) (Kg/m^2)	21.74	+	2.33	26.14	+	1.41	32.27	+	3.36
WC(a) (cm)	75.05	+	6.88	85.80	+	6.72	101.12	+	8.43
S BP(b) (mm Hg)	113.43	+	9.98	113.59	+	10.63	123.55	+	12.64
D BP(b) (mm Hg)	69.78	+	8.22	68.44	+	6.35	76.70	+	8.70
Hemoglobin (g/dL) (c)	14.76	+	0.98	14.83	+	0.90	14.74	+	0.74
TG (b) (mg/dl)	75.42	+	33.92	95.44	+	60.67	125.98	+	71.51
Cholesterol (b)	153.65	+	34.93	149.85	+	25.59	171.38	+	34.56
HDL-C(b) (mg/dl)	47.36	+	13.22	42.00	+	9.14	38.47	+	6.92
LDL-C(b) (mg/dl)	94.63	+	34.39	93.24	+	24.36	117.68	+	30.69
Ccr(c)[)](ml/min)	131.85	+	27.21	122.24	+	28.88	126.09	+	29.14
HOMA-IR(b)	1.25	+	0.71	1.30	+	0.59	2.68	+	2.07

SBP, systolic blood pressure, DBP diastolic blood pressure, HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; Data are mean ± standard deviation

(a) Significance found between each group

(b) Significance found in comparison of obese to normal weight and OW

(c) No significant differences found between any of the groups

Table 2. Clinical and Metabolic Characteristics according to the presence of OW/OB.

The prevalence of metabolic syndrome was 6.7% (13/195) overall, 0% in normal weight; 4.9% in OW and 23.4% in OB ($p<0.001$]. None had all 5 risk factors. None had diabetes. There was not a significant difference in the mean values of CrC between children with and without metabolic syndrome.

3.3. Hemoglobin quartiles

Subjects were divided for comparison of mean values of CrC, into four groups according to hemoglobin quartiles: 1st (12.2–14.1g/dL), 2nd (14.2–14.7 g/dL), 3rd (14.8-15.3 g/dL), and 4th (15.4–17.6 g/dL). None of the adolescents had anemia (Hb<12g/dL). Mean CrC was significantly higher in quartile 1 than in quartiles 2, 3 and 4 (Figure 1).

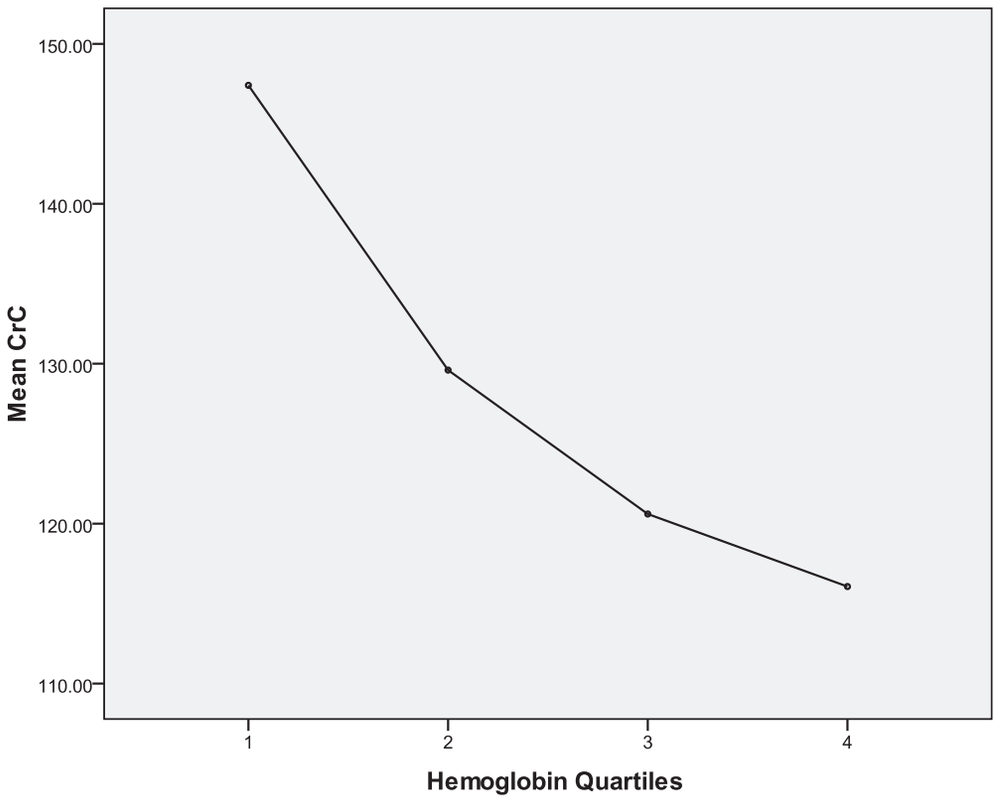

Figure 1. Mean Values of CrC according to Hemoglobin Quartiles

3.4. Insulin resistance quartiles

Subjects were divided into four groups by HOMA-IR quartiles for comparison of their means. As insulin resistance increased, BMI, waist circumference, systolic blood pressure, triglycerides and CrC increased significantly from the lowest to the highest quartiles of HOMA-IR levels (Table 3). There was not a significant difference in age, LDL-C, HDL-C, and total cholesterol between HOMA-IR quartiles.

3.5. Univariate and multivariate analysis

There was a univariate association ($p<0.01$) between CrC and age (r=--0.60), Tanner (r=-0.51), BMI (r = -0.29), waist circumference (r = -0.22), systolic blood pressure (r = -0.18), diastolic blood pressure (r =- 0.22), hemoglobin (r = -0.39), triglycerides (r = -0.15), insulin (r = 0.25), and HOMA-

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	Quartile I (0.14-0.87)			Quartile II (0.88-1.30)			Quartile III (1.31-1.85)			Quartile VI (1.9-9.80)		
	N=47			N=48			N=48			N=48		
Age (years) (e)	16.32	+	1.75	16.92	+	1.73	16.62	+	1.96	16.10	+	1.45
BMI[a] (Kg/m^2)	22.77	+	3.36	25.35	+	4.50	24.86	+	4.56	28.12	+	5.87
WC[a] (cm)	76.63	+	8.93	83.69	+	11.85	82.38	+	11.40	92.00	+	14.48
Systolic BP[b] (mmHg)	111.45	+	9.09	114.85	+	9.80	117.69	+	13.52	119.77	+	12.31
Triglycerides[c] (mg/dl)	67.17	+	28.89	84.71	+	46.94	91.42	+	46.68	125.46	+	73.76
Cholesterol(e) (mg/dl)	155.77	+	36.82	150.08	+	32.88	157.04	+	34.28	166.98	+	31.33
HDL-C(e) (mg/dl)	45.87	+	9.16	43.92	+	9.96	44.38	+	17.19	41.92	+	8.98
LDL-C(e) (mg/dl)	99.64	+	35.80	93.06	+	31.88	101.48	+	33.93	107.65	+	30.19
Ccr[c](ml/min)	122.33	+	19.78	119.16	+	28.22	133.83	+	31.93	137.28	+	27.30
Insulin(mU/l) (a)	3.21	+	1.05	5.46	+	1.03	7.65	+	1.07	14.34	+	7.93
HOMA-IR(a)	0.60	+	0.20	1.08	+	0.14	1.58	+	0.16	3.18	+	1.78

[a] Significance found in comparison of quartile I to II, and quartile IV to I,II &III

[b] Significance found in comparison of quartile I to III & IV

[c] Significance found in comparison of quartile IV to I,II &III

[d] Significance found in comparison of quartile I to III and quartile IV to I,II &III

[e] No significance found between any of the groups

Table 3. Clinical and metabolic patient characteristics according to HOMA-IR quartiles. Analysis by analysis of variance: mean (± SD)

IR (r = 0.24). There was neither a significant correlation between CrC and white leukocytes count, nor with HDL-C.

When significant factors chosen by univariate analysis were entered in the multiple linear regression analysis, it showed that age, BMI, hemoglobin and HOMA-IR were significantly associated with CrC adjusted for Tanner stage, waist circumference, systolic, diastolic blood pressure, and triglycerides (r^2=0.52) (Table 4). In order to obtain an r^2 in each step, a stepwise method was used. The first step, which incorporated only age, explained 37% of the total variance. The second step, which included hemoglobin, produced an increase of 6% and the third step which included BMI, produced an increase of 3%. The fourth step, which included HOMA-IR, produced an increase of 6% of the variance, reaching 52%.

	Unstandardized Coefficients		T	Significance	R^2
	B	Std. Error			
Age	-5.84	1.06	-5.50	<0.001	0.52
BMI	-1.86	0.41	-4.49	<0.001	
Hb	-6.93	1.91	-3.64	<0.001	
HOMA-IR	6.40	1.47	4.36	<0.001	

Table 4. Multiple Regression Analysis (stepwise method)

Dependent variable: CrC. Adjusted for waist circumference, Tanner stage. systolic blood pressure, diastolic BP, triglycerides.

4. Discussion

The most important findings in this report were that age, insulin-resistance, BMI, and hemoglobin were associated with CrC in normal adolescents. These findings were supported by the results of the univariate correlations and the multiple regression analysis with the use of lipid profile, blood pressure, and waist circumference as independent factors. Adolescents with insulin-resistance had a higher CrC compared to adolescents without insulin-resistance of a similar age and pubertal development. We also found that mean CrC was significantly higher in adolescents in the lower hemoglobin quartile than in the other quartiles.

The rise in the prevalence of OW/OB in adolescents is one of the most alarming public health issues facing the world today. The 2003-2004 US National Health and Nutrition Examination Survey of adolescents aged 12 to 19 years found that 35% of children were OW/OB [25]. The prevalence of OW/OB in this cohort of Argentinean adolescents (45.1%) was higher than the high rate of OW/OB among adolescents in the United States. This could be due to the fact that OW/OB adolescents are especially encouraged to practice a sport. Furthermore, bigger adolescents are specially selected for certain positions on the rugby field due to their size. Therefore, the prevalence of OW/OB in this group of rugby amateurs could be overrepresented.

Clinical and pathologic characteristics of a distinct nephropathy have emerged independent of that of diabetic or hypertensive glomerulosclerosis including a silent presentation in OB individuals [26-28]. Tomaszewski et al. [29] was the first to demonstrate that OB could explain the relationship between hyperfiltration and BMI. However, as Cockcroft–Gault equation was used to estimate glomerular filtration rate, it introduced a major methodological problem since weight was included in the formula [29]. Consistent with this study, several papers showed that OB was associated with elevated glomerular filtration rate [30-,33]. In contrast several studies [34,35] noted that glomerular filtration rate in OB patients was lower. The mechanism could be due to increased fat in the renal helium that may compress renal vessels and parenchyma, decreasing renal blood flow and tubular flow rates [34,35]. Consistent with these

studies this paper shows a significant inverse association between BMI and glomerular filtration rate in healthy adolescents. Therefore, increased renal blood flow and hyperfiltration may not be universal findings in OB individuals. The potential mechanisms involving OB and CrC are perhaps unknown [10].

A recent retrospective cohort study showed that BMI was an independent predictor of chronic kidney disease progression on multivariate analysis but no significant difference was observed between normal weight and OW/OB individuals [36]. Another methodological issue is the categorization of individuals as OW or OB. Consistent with this fact, though we found that mean CrC was higher in the normal weight than in OW/ OB adolescents the difference did not reach a significant level. However, we found a significant inverse association between BMI and glomerular filtration rate in the univariate and in the multivariate analysis.

Insulin resistance has been implicated as a predictor of renal function [11,37,38]. The National Health and Nutrition Examination Study (NHANES) III population [11] showed that after adjustment for multiple confounders, the odds ratios of prevalent kidney disease significantly increased from the lowest to the highest quartiles of HOMA-IR. Consistent with these studies we found that CrC increased as HOMA-IR quartiles increased. Our findings are also in accordance with previous community-based studies in adults [11, 38] which have investigated the association of insulin resistance and CrC. Impaired insulin sensitivity and hyperinsulinemia have been suggested to contribute to the development of renal injury via a number of different pathophysiologic pathways. Insulin per se stimulates the expression and activation of IGF-1, and components of the renin-angiotensin-aldosterone system [39]. These factors have been shown to promote mitogenic and fibrotic processes in the kidney, such as proliferation of mesangial cells and extracellular matrix expansion [39]. Moreover, insulin resistance and hyperinsulinemia are closely associated with oxidative stress [40], which could promote renal injury via decreased production and availability of nitric oxide [41]

Our study shows that hemoglobin was inversely associated with CrC. Different studies performed to investigate the risk factors of chronic kidney disease in communities showed that OB, and anemia, were positively correlated with the development of the disease [7,8]. This research found that adolescents in the lower quartile of hemoglobin had significantly higher mean CrC than adolescents in the other quartiles, even if none of the adolescents had anemia. Consistent with these previous studies we found in the regression analysis that there was a significant inverse association between CrC and hemoglobin, adjusted by several confounding factors.

Several limitations of this study should be acknowledged. First, it was a cross-sectional analysis, and thus, the directionality of the associations could not be established. However, appropriate analysis of cross-sectional data represent a useful initial step in identifying relationships between OB and CrC. Secondly, CrC was estimated with serum creatinine and not with the gold standard measure of renal function [21] Therefore, an incorrect conclusion may derive from our results. Thirdly, as the sample included only adolescent boys, girls were not represented. However, the strengths of our study included our amateur rugby club sample, which was more likely to represent the healthy population, the good response rate of the adolescents, the measurement of creatinine concentration for all participants by the same

laboratory and method, and the use of regression models and simultaneous adjustments of confounding variables.

5. Conclusions

In summary, we have identified BMI, hemoglobin and insulin-resistance as strong and potentially modifiable risk factors for the development of chronic kidney disease in adolescents. Therefore, efforts to prevent and treat OB and insulin resistance in the general population could possibly have a beneficial impact on the incidence, progression and related co-morbidities and costs of chronic kidney disease. However, further longitudinal studies are needed in order to shed further light on this issue.

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