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Hyperinsulinemia and Insulin Resistance in Pediatric Patients with Chronic Kidney Disease

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Abstract

Background: Pediatric chronic kidney disease (CKD) is associated with disturbance of glucose metabolism & insulin receptor sensitivity leading to impaired glucose tolerance & insulin resistance (IR), which are potential risk factors for cardiovascular disease (CVD). Hyperinsulinemia and IR are not extensively investigated in children with CKD, especially in different stages of CKD.

Aim of Study: Detect hyperinsulinemia & IR in pediatric CKD patients.

Subjects and Methods: A total of 87 children and adolescents; 58 with chronic kidney disease (CKD); (29 CKD stage 2-4, pre-dialysis group & 29 CKD stage 5 on regular hemodialysis, CKD5d group) & 29 age & gender matched controls were enrolled in the current cross-sectional study. Homeostasis model assessment of insulin resistance (HOMA-IR) using fasting insulin & glucose, where IR was considered if HOMA-IR was ≥4.39.

Results: Fasting insulin & glucose hadn't significantly changed between CKD patients & controls (p=0.7, 0.3 respectively), while IR represented by HOMA-IR was found in a total of 11 (12.6%) CKD patients (6, 6.89% CKD5d & 5, 5.74% CKD 2-4) with no significant difference between pre-dialysis & dialysis groups (p>0.05), while it was significant with controls (p=0.039), meanwhile, the total means of HOMA-IR between were no statistically significant between all CKD patients & (p=0.64). HOMA-IR correlated positively to dialysis durations (p=<0.001, <0.001 respectively), but hadn't changed with BMI.

Conclusion: Pre-dialysis & dialysis CKD pediatric patients are at a high risk of IR & hence CVD. CKD & dialysis durations are independent risk factors for IR.

Key Words: *BMI – CKD – HOMA-IR – IR.*

Introduction

CHILDREN with chronic kidney disease (CKD) carry the highest risk for cardiovascular disease (CVD) which are multifactorial, not only limited to uremia-related risk factors, but also to hypertension, dyslipidemia, and altered glucose metabolism [1]. It has been found that insulin resistance developed with decreased renal functions, also many factors contribute to its development such as untreated anemia, erythropoietin deficiency, uremic toxins, exercise intolerance, vitamin D deficiency and inflammation in addition to dialysis inadequacy, which all play an important role inoxidative stress and inflammation; contributing to development of cardiovascular diseases [2]. In pediatric patients with CKD, the presence of glucose intolerance and insulin resistance may also be potential risk factors for CVD, as in adult patients [3]. Hyperinsulinemia and insulin resistance are not extensively investigated in children with CKD as in adult especially in the Egyptian population.

Aim of the work: Screening of fasting insulin status & detect insulin resistance (IR) by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in pediatric CKD 5 patients on regular hemodialysis.

Subjects and Methods

A cross-sectional study that was carried out at pediatric dialysis & nephrology unit, children hospital, Ain Shams University, on 58 CKD pediatric patients (29 CKD stage 2-4 & 29 stage 5 on regular hemodialysis, CKD5d) and 29 age and sex matched controls. Patients known with diabetes mellitus (DM) or positive family history of type 1 DM (T1DM) were excluded from the start. On examination, no one had acanthosis nigricans. Careful medical history was taken in the form of age, sex, durations of the disease & dialysis. Assay of fasting insulin & fasting glucose were done by withdrawing 3ml of blood serum (was withdrawn before dialysis session in dialysis group) after fasting for 8 hours, where specimens were analyzed by Roche Modular P chemistry analyzer (Roche

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Diagnostics, 9115 Hague Road, Indianapolis, IN 46250). Hyperinsulinemia was defined as fasting insulin levels ≥15 mU/ml [4]. HOMA-IRusing fasting insulin & fasting glucose for the equation of [fasting insulin ([illegible]U/ml) x fasting plasma glucose (mg/dl)]/405], where IR was considered if HOMA-IR ≥4.39 (upper 2.5 percentiles or >2 SDs above mean HOMA-IR for normal-weight children) [5]. Both oral and written consents were obtained from patients and their caregivers according to the guidelines of Institutional Review Board (IRB) of college of medicine with approval number of FMASU M S 330 / 2020.

Results

This study had 58 CKD pediatric patients (29 with CKD2-4 or pre-dialysis & 29 CKD5 or dialysis) & 29 age & gender matched children as controls, where the mean age was 9.41 ±3.66, 10.62 ±2.21, 9.03±2.24 years respectively (p=0.083). The median body mass index standard deviation score (BMI SDS) was significantly lower in dialysis group compared to pre-dialysis & controls (p=0.001), while median dialysis duration was 3 (1-7) years (Table 1). We had total 11 (18.96%) CKD patients with hyperinsulinemia (5, 8.66% CKD 2-4, 6, 10.34% CKD5d), while the median fasting insulin inulU/ml was 6.2 (2.7-10) in CKD5d patients, 7.7 (6.4-8.6) in CKD2-4 & 4.9 (2.8-11.9) in controls, with no significant difference (p=0.7). Fasting glucose was >120mg/dl in 4 (6.8%) CKD2-4 patients, 2 (3.4%) CKD5d, & no one in controls, while the mean fasting glucose was 96.03 ±23.88, 93.45±20.89 & 88.52±7.88mg/dl respectively, with no statically significant difference between all of them (p=0.31). We had 11 (12.64%) CKD pediatric patients with insulin resistance as defined by HOMA-IR >4.39, where 6 (6.89%) patients CKD5d & 5 (5.7%) patients CKD2-4, while no one in controls, with significant difference between both CKD groups & controls (p=0.039), nevertheless, the baseline median HOMAR-IR was insignificantly differed between all the 3 groups (p=0.64); (Table 2). On studying the correlation of HOMA-IR & other variables, it was positively correlated with dialysis durations (r=0.751, p<0.001), where insulin resistance increased with the longer dialysis duration, while the BMI had no associations (Table 3).

Table (1): Demographic data in studied groups.

Variables	Groups			Test of significance	
	Control (no.=29)	CKD5d (no.=29)	CKD2-4 (no.=29)		
	Mean ± SD Median (range) no. (%)	Mean ± SD Median (range) no. (%)	Mean ± SD Median (range) no. (%)	Value	p-value
Age (year)	9.03±2.24	10.62 ± 2.21	9.41 ± 3.66	f=2.56	0.083
Gender:					
Male	15 (51.72%)	13 (44.83%)	13 (44.83%)	X^2=0.36	0.832
Female	14 (48.28%)	16 (55.17%)	16 (55.17%)		
BMI SDS	0.67 (0-1.81)	–0.82 (–2.68 - 0.5)	0.96 (–1.01 - 2.01)	H=13.23	0.001 (K1)
Hemodialysis duration (Year)		3 (1 - 7)			

BMI SDS: Body mass index standard deviation score. (f): *One Way ANOVA test of significance. (H): *Kruskal Wallis test of significance.
*Post-hoc test was significant between: (K1) CKD5d group Vs. (Control and CKD2-4 groups). (X^2): *Chi-Square test of significance.

Table (2): Fasting insulin, glucose & IR in studied groups.

Variables	Groups			Test of significance	
	Control (no.=29)	CKD5d (no.=29)	CKD2-4 (no.=29)		
	Mean ± SD Median (range) no. (%)	Mean ± SD Median (range) no. (%)	Mean ± SD Median (range) no. (%)	Value	p-value
Fasting Insulin (ulU/mL)	7.7 (6.4-8.6)	4.9 (2.8-11.9)	6.2 (2.7-10)	H=0.712	0.7
Fasting Glucose (mg/dL)	88.52±7.88	93.45±20.89	96.03±23.88	f=1.187	0.310
HOMAIR	1.68 (1.36-1.9)	1.15 (0.54-3.09)	1.36 (0.61-2.33)	H=0.868	0.648
IR (HOMA-IR>4.39):					
No	29 (100%)	23 (79.31 %)	24 (82.75%)	Fisher's Exact test	0.039 (K1)
Yes	0 (0%)	6 (20.68%)	5 (17.25%)		

(f) : *One Way ANOVA test of significance. (H): *Kruskal Wallis test of significance.
*Post-hoc test was significant between: (K1) CKD5d group Vs. (Control and CKD2-4 groups).

Table (3): Correlation analyses (Spearman's correlation) of HOMA-IR (and other variable factors.

HOMA-IR	Spearman's rho	p–value
BMI SDS	–0.068	0.612
Hemodialysis duration (Year)	0.751	<0.001

BMI SDS: Body mass index standard deviation score.

Discussion

Insulin resistance is a well-known complication of CKD, which occurs as a diminished response of target organs to the insulin effect. The mainfunction of insulin is enhancing the glucose uptake by skeletal muscles, decreased hepatic glucose production & lipolysis in adipose tissues **[6,7]**.

We had total 11 (12.64%) CKD patients with insulin resistance (5, 5.7% CKD2-4, 6, 6.89% CKD5d), while no one in the control group. No significant difference could be found between both pre-dialysis & dialysis groups (p>0.05), with statistically significant difference when compared tocontrols (p=0.011), meanwhile, the median fasting insulin, glucose & HOMA-IR showed no significant difference between all the 3 groups (p=0.7, 0.31, 0.64). Our study was in accordancewith study by **[8]** , who compared pre-dialysis, dialysis patients & controls in terms of insulin resistance using HOMA-IR, where insulin resistance was found in 82.80%, 80.60% & 00.00% respectively with significant difference among all the 3 groups (p=0.02), nevertheless our results were in discordant to their results regarding the mean insulin values and HOMA-IR indexes, where significantly higher values were found in the pre-dialysis and dialysis patient groups compared to the controls (p=0.019, p=0.014; respectively). Pediatric studies by (9&10) had also demonstrated a high prevalence of abnormal results of glucose tolerance tests (32.7%, 45% respectively) and increased HOMA-IR (47.1%) in CKD children before renal transplantation.

The study revealed that IR had not correlated significantly with BMI (p=0.90, 0.073, 0.61 respectively). This could be explained by the direct effect of the kidney disease itself on insulin receptors & dysregulation of glucose metabolism, rather than the known metabolic syndrome that is associated with obesity & high BMI as in usual population, thus, it renders the CKD pediatric patients to the risk of non-obese metabolically obese variant (NOMO) which increases the cardiovascular risk through a mechanistic pathway independent of fat metabolism. A study by **[11]** that was conducted on children and adolescents with CKD, found frequent hyperinsulinemia and insulin resistance in children with mild-to-moderate CKD, which was similar to our results, however it disagreed with ours in the form of association with BMI, where they found that HOMA-IR was strongly associated positively with high BMI, where abnormally high HOMA-IR was found in six (40%) non-lean subjects and in only one lean subject (p<0.001).

Our results showed a significantly positive correlation between HOMA-IR with the total duration of dialysis (r=0.751, p<0.001), where insulin resistance increased with the longer dialysis duration, which could be explained by the effect of disease & dialysis on sensitivity ofinsulin receptors & dysregulatedglucose metabolic pathway **[12]** found similar findings where HOMA-IR was an independent predictor of carotid stiffness on analysis, including age, BMI, duration of dialysis & blood pressure.

Conclusions and Recommendations:

In conclusion, predialysis & dialysis CKD pediatric patients are at a high risk of IR & hence CVD. Dialysis durations is an independent risk factor for IR; however, BMI had no correlation. We do recommend the importance of frequent monitoring insulin levels in pediatric patients with chronic kidney disease for early interventionto avoid cardiovascular disease & increased mortality.

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فرط الأنسولين فى الدم ومقاومة الأنسولين فى المرضى الأطفال الذين يعانون من أمراض الكلى المزمنة

\الخلفية: يرتبط مرض القصور الكلوى المزمن (CKD) لدى الأطفال باضطراب أيض الجلوكوز وحساسية مستقبلات الأنسولين مما يؤدى إلى ضعف تحمل الجلوكوز ومقاومة الأنسولين (IR)، وهى عامل خطير لأمراض القلب والأوعية الدموية (CVD). لم تم دراسة فرط الأنسولين فى الدم على نطاق واسع وخاصة فى الأطفال المصابين بمرض القصور الكلوى المزمن، وخاصة فى مراحل لها مختلفة.

\الموضوعات والأساليب: مجموعة من ٨٧ طفلاً ومراهقاً يعانون من مرض القصور الكلوى المزمن (CKD)، (٢٩ مرحلة CKD ٢–٤، مجموعة ما قبل غسيل الكلى و٢٩ CKD المرحلة ٥، مجموعة غسيل الكلى) و ٢٩ آخرين تم اختيارهم بناءا على الضوابط المطابقة للعمر والجنس فى الدراسة المقطعية الحالية. تم تقييم نموذج التوازن لمقاومة الأنسولين (IR-HOMA) باستخدام الأنسولين والجلوكوز أثناء الصيام، حيث تم التشخيص إذا كان IR ≥-HOMA ٤.٣٩.

\الهدف: الكشف عن فرط الأنسولين فى الدم فى الأطفال مرضى القصور الكلوى المزمن.

\النتائج: لم يتغير نسبة الأنسولين والجلوكوز الصائم بشكل كبير بين مرضى القصور الكلوى المزمن (CKD2-4 & CKD5d) وبين الضوابط (p=٠.٧، ٠.٣ على التوالى)، فى حين تم تشخيص مقاومة الأنسولين ممثلة فى IR-HOMA فى ١١ (١٢.٦٪) مريض قصور كلوى مزمن (٦، ٦.٨٩٪ CKD5d و ٥، ٥.٧٤٪ CKD2-4) مع عدم وجود فرق كبير بين مجموعة غسيل الكلوى ومجموعة ما قبل الغسيل (p<٠.٠٥)، فى حين كان هناك فرق كبير مع الضوابط (p=٠.٠٣٩) وفى الو قت نفسه، لم تكن الوسائل الإجمالية ل IR-HOMA بين جميع جميع مرض القصور الكلوى المزمن (CKD) ذات دلالة إحصائية (p=٠.٤٦) ارتبط IR-HOMA بشكل إيجابى بالفترة الزمنية للغسيل الكلوى (p<٠.٠٠١، ٠.٠٠١ على التوالى)، لكنه لم يتغير مع مؤشر كتلة الجسم.

\الاستنتاج: الأطفال المرضى بالقصور الكلوى المزمن (CKD) هم فى خطر كبير من مرض مقاومة الأنسولين (IR-HOMA) وبالتالى الأمراض القلبية الوعائية. المدة الزمنية للمرض والغسيل الكلوى هم أهم عوامل التأثير.