Original Research Article

The Effect of Chromium in The Pathogenesis of Insulin Resistance in Preeclampsia

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Abstract
Insulin resistance is well established to be related with preeclampsia. The action of insulin in human appears to be potentiated by chromium. The aim of present study was assessment of chromium level in the development of insulin resistance in preeclampsia and hence its pathogenesis.

This case control study was achieved on subjects recruited from Babylon Teaching Hospital for Obstetric & Gynecology during the period between September 2013 till October 2015, included 90 pregnant women, 45 of them identified with preeclampsia in the third trimester and other 45 were apparently healthy pregnant women taken as a controls.

Chromium concentrations was measured by Atomic Absorption Spectrophotometry. Fasting insulin was estimated by Enzyme Linked Fluoroscent Immune-Assay (ELFA) technique and fasting plasma glucose concentration by glucose oxidase method. Insulin resistance was calculated by homeostatic model assessment (HOMA) using mathematical equation.

The results of present study showed no significant difference in fasting plasma glucose concentrations between patients and controls (P value >0.05), while there were a significant differences in chromium concentration level and insulin resistance between two groups (P value <0.05). However, there was no correlation between insulin resistance in patients with preeclampsia and low chromium level (r= 0.101, p=0.508).

The present study concluded that low chromium level has no impact on the development of insulin resistance in preeclampsia.

Key Words: Preeclampsia, Chromium, Insulin resistance, HOMA, Fasting plasma glucose

تأثیر الكروم في التسبب في مقاومة الأنسولين في تسمم الحمل
تأثیر مستوى الكروم على مقاومة الأنسولين في مرض تسمم الحمل

الخلاصة
من المعروف إن زيادة مقاومة الأنسولين مرتبطة بمرض تسمم الحمل وإن عمل الأنسولين في الإنسان مرتبطة بالكروم. كان الهدف من هذه الدراسة هو تقييم مستوى الكروم في نشوء مقاومة الأنسولين وبالتالي حدوث مرض تسمم الحمل.

أجريت هذه الدراسة في مستشفى بابل التعليمي للأمراض الشائعة وطب الأطفال في مدينة الحلة خلال الفترة ما بين أيلول عام 2013م وحتى تشرين الأول من عام 2015م، وشملت الدراسة 90 امرأة حامل، 45منهن مصابة بمرض تسمم الحمل ونائيات غير مصابات تم أخذهم معاً بمثابة مصيّرات. تم قياس الكروم بواسطة جهاز الأنسولين الاستشعاري وقياس مستوي الأنسولين عند الصوم بتقنية إینزيم الكروموكسيدزا. ثم حساب مقاومة الأنسولين بمعالجة رياضية.

أظهرت نتائج الدراسة بأنه لا يوجد فرق معنوي في مستوي الكروم عند الصوم بين النساء الحاملن المصابات بمرض تسمم الحمل والإناث غير مصابات (نسبة الاحتمالية أكثر من 5%). كما أظهرت الدراسة أن هناك فرق معنوي في مستوي الكروم ومقاومة الأنسولين بين المجموعتين (نسبة الاحتمالية أقل من 5%). ومع ذلك لم تكن هناك علاقة بين مستوى الكروم ومقاومة الأنسولين.

خلصت هذه الدراسة بأن الكروم ليس له تأثير على نشوء مقاومة الأنسولين في مرض تسمم الحمل.
Introduction

Preeclampsia (PE) is characterized by hypertension and proteinuria occurring after the twentieth week of gestation in a previously normotensive woman and completely disappear by the sixth postpartum week[1]. Complications of PE and accompanied pathologies have become one of the most important causes of maternal and fetal morbidity and mortality in the world, leading to about 40% of births delivered before 35 weeks of gestation. Furthermore, PE has been strongly related to an increased risk of later-life death due to cardiovascular disease, independent of other risk factors. The incidence of PE is around 5–10% of all pregnant women worldwide and despite the amount of resources spent in the research and treatment of this pathology, its development is still barely predictable and thus challenging to prevent and manage clinically[2].

The physio-pathological process of PE starts with inadequate trophoblast invasion early in pregnancy, which causes an increase in oxidative stress leading to the development of systemic endothelial dysfunction in the later phases of the disease, and consequently to the characteristic clinical manifestation of PE, with hypertension, proteinuria, and edema[3].

Increased insulin resistance (IR) is well established to be related with PE. There are several opinions to demonstrate this relationship. Elevated insulin increases sympathetic tone and muscle blood flow and also in chronic conditions (unlikely relevant to PE) increases vascular smooth muscle growth. IR is likely to be involved in the pathogenesis of PE rather than being caused by PE[4].

Increased IR can stimulate the sympathetic nervous system and cause an increase in expression of receptors for endothelin, both of which events lead to increased blood pressure. Hyper-insulinemia can also produce hypertri-glyceridemia, leading to endothelial dysfunction and decrease production of prostacyclin.

This hyperinsulinemia can remain for as long as 17 years after preeclamptic pregnancy and may contribute to a woman's increased risk of cardiovascular disease[5,6]. Chromium (Cr) is an element occurred naturally in animals, plants, rocks, and soil. It can present in several entities. The most common are Cr (0), Cr(III), and Cr (VI), which is also known as hexavalent Cr[7].

The main biological role of Cr in human appears to potentiate the action of insulin, as part of a low molecular weight chromium binding substance (chromodulin). Cr may also be important in gene expression, lipoprotein metabolism and in maintaining nucleic acid structure[8,9].

The aim of this study was to assess the role of Cr level in the development of IR in PE and hence its pathogenesis.

Materials and Methods

This case control study was achieved on subjects recruited from Babylon Teaching Hospital for Obstetrics & Gynaecology, City of Hilla. Samples were obtained during the period between September 2013 till October 2015, included 90 pregnant women, 45 of them identified with PE by gynecologist expert in the third trimester and other 45 were apparently healthy pregnant women taken as a controls in the same period of pregnancy.

Complete evaluation of pregnant women was undertaken which involve history, physical examination, laboratory investigations, and ultrasound. Pregnant women more than 40 years old, body mass index > 30, smoking, prior history of PE, family history of PE, prior hypertension or kidney disease, previous history of vascular disease, and multiple pregnancy were excluded from this study.

The anthropometric measurements involving age, gestational age, and body mass index of PE group were comparable to control group, where there was no significant differences (P>0.05).
Ethical considerations
Acceptance of scientific committee of the Clinical Biochemistry Department/College of Medicine/University of Babylon and permission of Babylon Health Directorate/Ministry of Health & Information Center for Research & Development of Babylon Province/Iraq were taken.
The aims were informed to all contributors involved in this study and verbal consent had been taken.

Samples collection
Venous blood samples were aspirated from studied group after 5 hours fast. Five ml of blood were obtained from each subjects by vein puncture, put in heparin containing tube, then centrifuged at 2000×g for approximately 5 minutes. plasma was used for measurement of fasting plasma glucose (FPG), fasting insulin (FI) level and Cr concentration.

Determination of chromium, fasting plasma glucose and fasting insulin Cones:
Cr concentrations was estimated by Furnace Graphite Atomic Absorption Spectrometer provided by PG Instruments Ltd (United Kingdom) with usage of Cr hollow cathode lamps supplied by Varian. FPG concentration was estimated by glucose oxidase method using a kit provided by Biolabo/France. FI was determined by Enzyme linked Fluoroscent Immune-Assay (ELFA) using AIA-360 Automated Immunoassay Analyzer from Tosoh Bioscience/Japan.

IR was calculated by HOMA-IR model using mathematical equation[10].

\[
\text{Fasting insulin(mIU/ml) x Fasting plasma glucose (mmol/L)}
\]

\[
\text{HOMA-IR =} \quad 22.5
\]

Statistical Analysis
Statistical analysis was achieved by using statistical package for social sciences (SPSS) 20th version. Quantitative data were presented as mean ± SD and independent sample t-test was used to compare between two groups. Chi square ($X^2$) test was used to find the significance of the categorical variables and Pearson’s correlation was used to establish the relationships between variables. P-value of < 0.05 was considered to be statistically significant.

Result and Discussions
Several studies have investigated the role of IR in development of PE. In this study, we investigated whether PE is associated with plasma Cr level and whether it is a subsequent element for PE as it is an essential nutrient for the maintenance of normal glucose tolerance and its deficiency causes IR as presented by Ayling RM and Hua Y et al [8,11].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>No.</th>
<th>Mean</th>
<th>SD</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>Control</td>
<td>45</td>
<td>4.54</td>
<td>0.44</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>45</td>
<td>4.44</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>FI</td>
<td>Control</td>
<td>45</td>
<td>9.14</td>
<td>2.44</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>45</td>
<td>20.14</td>
<td>6.20</td>
<td></td>
</tr>
<tr>
<td>Cr</td>
<td>Control</td>
<td>45</td>
<td>0.51</td>
<td>0.08</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>45</td>
<td>0.31</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>Control</td>
<td>45</td>
<td>1.84</td>
<td>0.51</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Patient</td>
<td>45</td>
<td>3.95</td>
<td>1.26</td>
<td></td>
</tr>
</tbody>
</table>

*Significant differences
Table (1) showed no significant difference in FPG between patients and controls, P value >0.05 (both pre-eclamptic and normotensive women were able to dispose glucose equally) which may be attributed to significant difference in FI level as it is higher in patients rather than controls to compensate the significant higher IR presented in the same table for patients to alleviate glucose level. This finding agreed with the definition of compensatory hyperinsulinaemia presented in the review of Wilcox G [12] as it occurs when pancreatic β cell secretion increases to maintain normal blood glucose levels in the setting of peripheral IR in muscle and adipose tissue. This response is consistent also with a pregnancy-induced state of peripheral IR, the purpose of which is likely to ensure a sustained postprandial supply of glucose to the fetus as reported by Hauth J C [5].

Table (2) also showed a significant low Cr plasma level in patient group compared to control as it is a potential contributor to IR as presented by Hua Y et al [11], Wilcox G [12], Anderson RA [13] and Vladeva SV et al [14].

Table 2: Risk estimate of insulin resistance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Groups</th>
<th>Odds Ratio (95%) Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>Patients</td>
<td>Control</td>
</tr>
<tr>
<td>&lt; 2.5</td>
<td>43 (95.6)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>≥ 2.5</td>
<td>39 (86.7)</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.05*</td>
<td>139.33 (26.62-733.48)</td>
</tr>
</tbody>
</table>

*Significant differences

Table (2) revealed that the IR pregnant women were 139 times more susceptible to develop PE than non-IR pregnant women where 2.5 was taken as cut-off value for IR. This finding agreed with Hauth [5] who concluded that mid-trimester maternal IR is associated with subsequent PE. Berkowitz [15] reported that IR appears to be a causative mechanism for the development of essential hypertension. In the case of pregnancy, the temporary state of insulin resistance unmasks individuals with an early β-cell defect and allows for identification of high-risk groups at a time when therapeutic interventions could result in primary prevention of disease. Evidence is beginning to accumulate that PE is at least partially mediated by IR. It is reported also by Thadhani et al [16] that increased IR is well established to be associated with PE. Parrett et al [17] concluded that IR is likely to be involved in the pathogenesis of PE rather than being caused by PE.

Figure (1) showed that there was no correlation between IR in preeclamptic patients and low Cr level (r= 0.101, p=0.508). The present result is inconsistent with Hua Y et al [11] who reported that there is a causative relationship between low Cr level and IR in diabetic patients. However, this inconsistency might be due to the difference in the nature of IR between diabetic and preeclamptic patients. In diabetes although the mechanisms underlying IR are not completely understood, it is thought to result, at least in part, from impaired insulin-dependent PI3K activation and downstream signaling as reported by Sinha et al [18]. This mechanism is alleviated by Cr as illustrated in the figure (2) Hua et al [11].
Figure 1: Correlation of I.R with S. Chromium among patients

Figure 2: Putative mechanisms by which chromium augments cellular glucose uptake
While in PE the IR regarded as adaptive mechanism that is activated in pregnancy to promotes reallocation of energy-rich substrates (glucose to the brain, fetus and immune system; fat to the fetus and the organs) and the compensatory hyper-insulinemia as reported by Zhou [19]. The activation of inflammatory system that happen in PE as a result of the dysfunction of the immunological system can aggravate placental IR leading to an over-expression of N-glycosylation and P-type (P-IPG) as a counter regulatory mechanism to IR. Furthermore, the lipemic fraction of P-IPG was appeared to be similar to endotoxins, and may serve as the link between IR, systemic inflammation and increased angiogenic factors as reported by Scioscia et al [20].

**Conclusion**

Low chromium level has no effect on the development of insulin resistance in preeclampsia.

**References**


