

Effect of human insulin and insulin analogue on some inflammatory markers and total antioxidant capacity in a sample of Iraqi type 1 diabetic children and adolescents

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Abstract

Background: Both human insulin and insulin analogue used in the treatment of type 1 diabetes mellitus. The modification in amino acids sequences of human insulin lead to produce analogue form which have a pharmacokinetic and pharmacodynamics effect near to normal human endogenous

insulin release.

Aim of study: This study designed to compare between the effect of each type of insulin on high sensitive C-reactive protein and interleukin-6 and total antioxidant capacity in a sample of Iraqi type 1 diabetic children and adolescents.

Study design: The study was enrolled on fifty-one Iraqi type 1 diabetic children and adolescence age range (6-18) year. The patients allocated into two groups, Group (1) includes 20 patients assigned to receive conventional human insulin (regular and NPH), and Group (2) includes 20 patients assigned to receive insulin analogue (insulin aspart and glargine) for three months. The inflammatory and antioxidant markers measured at baseline and after three months of intervention.

Results: After three months of treatment, both insulin groups did not affect high sensitive C-reactive protein (hs-CRP) significantly from baseline to 3 months. Only insulin analogue reduced Interleukin-6 (IL-6) significantly, while human insulin reduced level of IL-6 but it was not statistically significant. Both therapies reduced total antioxidant capacity (TAOC) significantly; however, insulin analogue had higher reduction percentage (15.1% vs. 5.7%) compared to the conventional insulin.

Conclusion: Only insulin analogue reduced IL-6 significantly. Both types of insulins did not effect on hs-CRP. Both therapies reduce TAOC significantly.

Key words: human insulin, insulin analogue, hs-CRP, IL-6, TAOC

تأثير الأنسولين البشري ونظير الأنسولين على بعض المؤشرات الالتهابية وقدرة مضادات الأكسدة الكلية في عينة من الأطفال والمراهقين العراقيين المصابين بالسكري من النوع الأول
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الخلاصة:

الخلفية: كل من الأنسولين البشري ونظير الأنسولين المستخدم في علاج داء السكري من النوع الأول. يؤدي التغيير في تسلسل الأحماض الأمينية للأنسولين البشري إلى إنتاج شكل تناظري له تأثير حركي وديناميكيات دوائية قريب من إطلاق الأنسولين الطبيعي البشري.

هدف الدراسة: صممت هذه الدراسة للمقارنة بين تأثير كل نوع من أنواع الأنسولين على بروتين سي التفاعلي عالي الحساسية والإنترلوكين-6 والقدرة الكلية المضادة للأكسدة في عينة من الأطفال والمراهقين العراقيين المصابين بالسكري من النوع الأول.

تصميم الدراسة: تم تطبيق الدراسة على واحد وخمسين طفلاً عراقياً من النوع الأول مصاب بالسكري تتراوح أعمارهم بين (6-18) سنة، تم تقسيم المرضى إلى مجموعتين، المجموعة الأولى تضم 20 مريضاً تم تعيينهم لتلقي الأنسولين البشري التقليدي (العادي و NPH)، وتشمل المجموعة الثانية 20 مريضاً تم تعيينهم لتلقي الأنسولين التناظري (الأنسولين aspart and glargine) لمدة ثلاثة أشهر. تم قياس علامات الالتهاب ومضادات الأكسدة عند البدء وبعد ثلاثة أشهر من استخدام العلاج.

النتائج: بعد ثلاثة أشهر من العلاج، لم تؤثر كلتا مجموعتي الأنسولين على بروتين سي التفاعلي عالي الحساسية (hs-CRP) بشكل ملحوظ من بدء العلاج وبعد 3 أشهر. فقط الأنسولين التناظري قلل من الإنترلوكين 6 (IL-6) بشكل ملحوظ، في حين أن الأنسولين البشري خفض مستوى الإنترلوكين 6 لكنه لم يكن ذا دلالة إحصائية. كلا العلاجين قلل من قدرة مضادات الأكسدة الكلية (TAOC) بشكل كبير؛ ومع ذلك، فإن نظير الأنسولين كان له نسبة تخفيض أعلى (15.1% مقابل 5.7%) مقارنة بالأنسولين التقليدي.

الاستنتاجات: فقط نظير الأنسولين خفض IL-6 بشكل ملحوظ. كلا النوعين من الأنسولين لا يؤثران على hs-CRP. كلا العلاجين يقللان من TAOC بشكل كبير.

الكلمات المفتاحية: الأنسولين البشري، نظير الأنسولين، بروتين سي التفاعلي عالي الحساسية (hs CRP)، إنترلوكين 6، قدرة مضادات الأكسدة الكلية (TAOC)

Introduction:

Human insulin analogue was introduced in order to overcome or pass the undesirable side effect of human insulin for example: nocturnal hypoglycemia associated with basal NPH, multiple snacking and weight gain. In addition to optimize the bolus insulin injection time with food intake, furthermore to enhance physiological profile to resemble endogenous secretion. The knowledge of A.A sequence of insulin suggested the bioengineering to analogue form. The differences between human insulin and analogue are related to improve in pharmacokinetics with a little modification in A.A sequence [1]. The short and long acting analogue provide type 1 diabetic patients with the advantage of tight glycemic control with less hypoglycemia [2]. CRP is one of the acute phase proteins, the serum or plasma levels of which increase during common, nonspecific response to a wide variety of illnesses. Though the discovery of the elevated level of CRP in the serum is not specific for any particular disease, CRP is synthesized in the liver and usually is present as a trace constituent of serum or plasma at a level less than 0.3 mg/dl. It is a useful indicator

of inflammatory processes. Moreover, measurement of CRP by high sensitivity CRP (myoglobin, creatine kinase MB, troponin I and T), which are used to measure the danger of cardiovascular and peripheral vascular illness. Inflammation of the arteries may show a role in the heart disease, and HS-CRP can regulate heart disease risk in those with unnoticed heart disease and risk of problems for those who have already had a heart disease [3]. The cardiovascular complications of diabetes may be induced thrombosis and marked rise in inflammatory markers as hsCRP [4]. Interleukin 6 (IL-6), created as a defense response after injury or inflammation, production of IL-6 showed a pathological consequence on autoimmunity and chronic inflammation [5]. Interleukin-6 (IL-6) synthesized in response to inflammatory process related to insulin resistance [6]. IL-6 signals reduced with age [7]. Interleukin-6 (IL-6) is a key pathogenic cytokine in multiple autoimmune diseases, over several mechanisms comprising changed T cell trafficking showed that IL-6 targeted therapeutic intervention may benefit T1DM patients [8]. Long-standing diabetic complications are leading cause of morbidity and mortality [9], the highest source of death in T1DM is cardiovascular

disease due to early endothelial dysfunction and its pathophysiological precursor. Free radical creation with oxidative stress production related with hyperglycemia [10]. Oxidative stress process resulted from in equilibrium between reactive oxygen production and the biological protective mechanism [11]. Free radicals may join with diversity of biomolecules like, carbohydrates, lipids, nucleic acids, proteins, and macromolecules of connective tissue which cause cellular damage [12].

Patients and methods:

Patients in the study were classified into two groups:

Group 1: 25 patients receive insulin analogue (insulin aspart) at meal times and (insulin glargine) at night.

Group 2: 26 patients receive human insulin (soluble insulin at meal time) and

(Neutral Protamine Hagedorn (NPH) insulin twice daily).

All patients treated with insulin for three months; each patient has insulin dose according to his weight. Patients in each group were followed up after 3 months high sensitive C-reactive protein (HsCRP), interleukin-6 (IL-6), total antioxidant capacity (TAOC) were measured before, and after three months of treatment. Measurement of High Sensitive C-Reactive Protein, interleukin-6, and total antioxidant capacity by using ELISA kit. SPSS 20.0 software used to analyze the data. The differences considered significant if p value<0.05

Results:

Demographic data: There was no significant difference in the age, duration of disease and gender between both groups.as shown in table 1

Table (1): Demographic data:

	Human insulin group	Insulin analogue group	P value
Number	20	20	-
Age (years)	12.05 ± 4.06	12.45 ± 3.65	0.745
BMI (kg/m ²)	20.00 ± 4.57	20.00 ± 3.49	0.908
Duration of disease (years)	4.65 ± 3.21	3.78 ± 3.59	0.422
Gender			0.744
Female	12 (60%)	13 (65%)	
Male	8 (40%)	7 (35%)	
Independent t test, Chi square test, p value >0.05 non-significant, N (patients' number) = (40) Mean ±SD			

The effect of human insulin and insulin analogue on inflammatory markers (hs-CRP and IL-6) and antioxidant marker (TAOC):

Table 2 represented that both insulins did not change hsCRP significantly from baseline to 3 months. Only insulin analogue reduced IL-6 with significant difference p-value=0.03. Human insulin

reduced IL-6 without statistically significant. Both therapies reduced TAOC significantly; but TAOC is reduced by analogues better than human insulin p-

value=0.004. However, insulin analogue had a higher reduction percentage (15.1% vs. 5.7%) as illustrated in table 2 and figure 1.

Table (2): The effect of human insulin and insulin analogue on inflammatory markers and antioxidant capacity

Variable		At Baseline	After Three months	P- value
	Number	20	20	-
CRP	Human insulin	6.2 (1.8 – 14.2)	4.0 (0.8 – 14.3)	0.277 [NS]
	Insulin analogue	3.2 (0.9 – 6.3)	3.1 (0.9 – 8.4)	0.560 [NS]
	P-value	0.127[NS]	0.640[NS]	
IL-6	Human insulin	17.8 (9.1 – 27.7)	12.5 (9.3 – 28.9)	0.940 [NS]
	Insulin analogue	18.9 (9.7 – 35.3)	11.6 (6.4 – 35.2)	0.030 *[S]
	P-value	0.529[NS]	0.565[NS]	
TAOC	Human insulin	85.3 (71.8 – 111.4)	80.4 (67.0 – 105.8)	0.030*[S]
	Insulin analogue	91.0 (73.9 – 143.1)	77.3 (26.9 – 123.8)	0.004**[HS]
	P-value	0.565[NS]	0.565[NS]	

Wilcoxon rank test used to analyze the data

Data presented by median and IQR

[NS]=Non-Significant, * =Significant difference (p value <0.05), ** =Highly significant difference (p value <0.01)

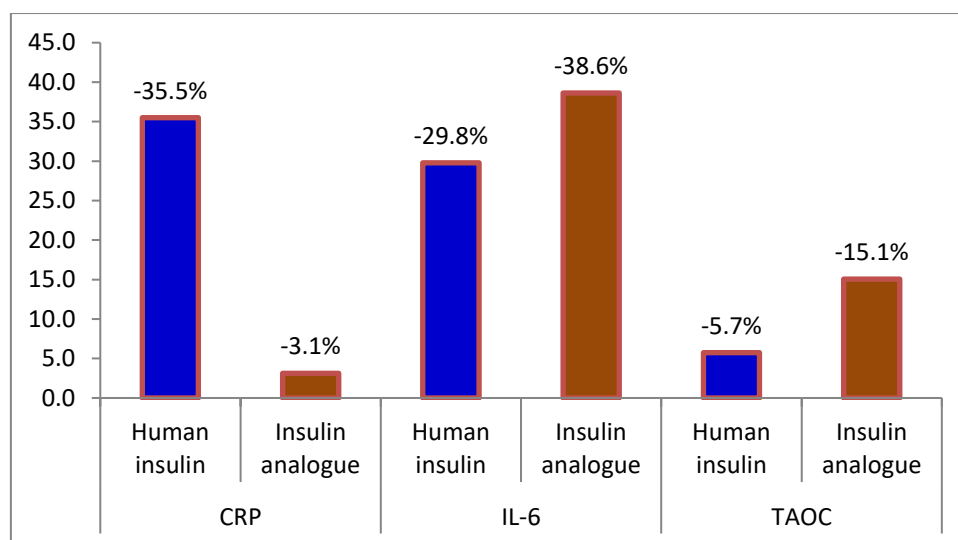


Figure (1): Percentage of reduction in median inflammatory markers and total anti-oxidant capacity for each insulin therapy

Discussion:

In the present study there is non-significant differences in hs-CRP in both groups at baseline and after 3 months of study since p value >0.05, these results not compatible with that obtained by Andras Treszl et al (2004) who studied the effect of insulin treatment in newly onset T1DM and he found that Insulin have anti-inflammatory effect, lead to downregulation of acute-phase protein creation of the liver

[13]consequently, it possibly will lead to reduce hcCRP concentrations [14]. Multiple studies numerate the role of IL-6 in T1DM; Alnek et al (2015) concluded that IL-6 diminished with age and have the tendency to be lower in spring compared to summer, although no difference was seen between T1DM patients and control group [15]. IL-6 levels as well nearly similar in young T1DM patients when compared to controls [16]. Erbağci AB et al (2001)

explored serum levels of C-reactive protein (CRP), interleukin (IL)-6, in T1DM children and they found that CRP and IL-6 were higher in diabetic patients. Serum CRP, lipids, Apo-lipoproteins and glycemic control were not significant predictors of cytokine concentrations in T1DM children, also higher systemic IL-6 were restricted to newly detected patients suggestive of early disease activation of the inflammatory immune markers [17]. IL-6 may affect glucose homeostasis indirectly by its action on adipocytes in skeletal muscles, beta cells of pancreas, hepatocytes, and neuroendocrine cells [18]. The present study showed reduction in TAOC after three months, this may suggest that both types of treatment may have an important role in disease improvement, consequently, minimize oxidative stress and total antioxidant capacity decrease. This may be explained by in vivo balance between oxidant and antioxidant capacity [19].

Conclusion: Only insulin analogue reduced IL-6 significantly. Both types of insulins did not effect on hs-CRP. Both therapies reduce TAOC significantly.

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