

Insulin effect on inflammatory response compared to sulfonylurea in diabetes mellitus patients

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Summary

This study was designed to state the ground stone of the role of the insulin as anti-inflammatory agent in different inflammation process.

Fasting venous blood samples were taken from 150 subjects of which 50 patients with type 1 diabetes, 50 patients with type 2 diabetes, and 50 healthy individuals.

All the blood samples were analyzed for F.B.S, HbA_{1c} %, TP, albumin, ESR, CRP, and immunoglobulin alpha₁-antitrypsine.

The present study results detected an increase in F.B.S, and HbA_{1c} % in sera of all patients of type 1 and type 2 compared for control.

Total protein levels showed no alteration in sera of both patients groups compared for control.

Decrease in albumin level was detected in sera of patient with type 2 group compared for patients with type 1 and control groups.

The factors for diagnosis of any type of inflammatory process ESR, CRP, alpha₁-antitrypsine were raised in patients with type 2 groups compared for patients with type 1 and control groups.

Key word: diabetes mellitus, insulin, sulfonylurea, acute phase protein

Introduction

Diabetes mellitus is actually a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both⁽¹⁾.

In 1979, the National Diabetes Data Group developed a classification and diagnosis scheme for diabetes mellitus. This scheme included dividing diabetes into two broad categories⁽²⁾ type1, insulin-dependent diabetes mellitus (IDDM), and type 2, non –insulin –dependent mellitus (NIDDM).

Type -1- constitutes only 10-20% of all diabetes and commonly occurs in childhood and adolescence⁽³⁾.

This disease is usually initiated by an environmental factor of infection (usually a virus) in individuals with a genetic predisposition and causes the immune destruction of the β cells of the pancreas and, therefore, a decreased production of insulin characteristics of type 1 diabetes include abrupt onset, insulin dependence, and ketosis tendency⁽⁴⁾.

Type - 2 diabetes is most commonly associated with obesity in middle-aged individuals. It is due to reduction in the number or affinity of insulin receptors on the plasma membrane of cells in target tissues, or an abnormal binding of insulin to the receptors⁽⁵⁾. Insulin is a peptide hormone composed of 51 amino acid residues and has a molecular weight of 5808 Da. It is produced in the pancreas, and released when any of several stimuli are detected. These include protein ingestion, and glucose in the blood⁽⁶⁾

Insulin causes most of the body's cells to take up glucose from the blood (including liver, muscle, and fat tissue cells), storing it as glycogen in the liver and muscle, and stops use of fat as an energy source. When insulin is absent (or low), glucose is not taken up by most body cells and the body begins to use fat as an energy source (i.e., transfer of lipids from adipose tissue to the liver for mobilization as an energy source). As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems (such as amino acid uptake by body cells)⁽⁷⁾

It has several other anabolic effects throughout the body. When control of insulin levels fail, diabetes mellitus results, insulin is used medically to treat some forms of diabetes mellitus. Patients with type 1 diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because the hormone is no longer produced internally. Patients with type 2 diabetes mellitus are insulin resistant, have relatively low insulin production, or both, some patients with type 2 diabetes may eventually require insulin when other medications fail to control blood glucose levels adequately⁽⁸⁾

The Drug (Daonil) is used as a second- generation sulfonylurea antidiabetic agent, appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. With chronic administration in type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug.

Sulfonylurea likely bind to ATP- sensitive potassium- channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage – sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin⁽⁹⁾

There are many actions of insulin on the global human metabolism level and on the cell, recently (Marc, et al, ⁽¹⁰⁾ found insulin to exert an anti inflammatory effect on cellular mediators and the hepatic acute-phase- response.

The total protein of the plasma is about 7.0-7.5 g/dL. The proteins of the plasma are actually a very complex mixture which includes not only simple proteins but also mixed or conjugated proteins such as glycoproteins and various type of lipoproteins in normal human plasma, six distinct moving boundaries have been identified. These are designated in order of decreasing mobility as albumin, alpha 1 and alpha 2 globulins, beta globulin, fibrinogen, and gamma globulin. ⁽¹¹⁾⁽¹²⁾

The levels of certain proteins in plasma increase during acute inflammatory states or secondary to certain types of tissue damage are called "acute phase proteins" or "reactants" and include C-Reactive protein (C.R.P), α 1-antitrypsin, haptoglobin, α 1-acid glycoprotein, and Fibrinogen⁽¹³⁾

CRP is one of the first acute phase proteins to rise in response to inflammatory disease. C - reactive protein (CRP) is synthesized in the liver and appears in the blood of patients with diverse inflammatory diseases⁽¹⁴⁾.

α 1-Antitrypsin is an acute-phase reactant. Its main function is to neutralize trypsin-like enzymes (i.e., elastase) that can cause hydrolytic damage to structural protein. α 1-Antitrypsin is a major component (approximately 90%) of the fraction of serum proteins that migrates electrophoretically immediately following albumin. Increased levels of α 1-antitrypsin are seen in inflammatory reactions⁽¹⁵⁾.

The Aim of this study

Evaluate the effect of insulin on some biochemical parameters related to acute phase proteins.

Sampling:

The samples were collected from "Al-Kadhimyah Teaching Hospital". They have been classified into three groups as the following:-

1-Control group: - include (30) healthy individual from both sexes, with age range (20-70) years and no previous disease which may interfere with the parameters analyzed in this study.

2-Type-1- (Insulin Dependent Diabetes Mellitus) IDDM group: include (50) patients from both sexes, with age range (20-60) years.

3-Type-2- (non-Insulin Dependent Diabetes Mellitus) NIDDM group: include (50) patients from both sexes, with age range (30-70) years.

Excluding criteria:-

Male patients suffer from infection of the renal tubules or fungus of the renal system.

Female patients were suffering from acute reproductive system infections.

All patients were not taking any non steroidal anti inflammatory, aspirin and statin drugs, also not taking Angiotension Converting Enzyme Inhibitor (ACEI) and anti-diabetic drug Thiazolidinediones (Glitazones).

Collection of Blood:

10 ml venous blood was taken from the above groups, placed in a plain tube (no anti coagulant) left for (15min) at room temperature, then centrifuged (at 2500 rpm for 10min). To get the serum, which is stored at (-20°C) unless used immediately. Whole blood was used for ESR and HbA_{1c} determination.

Determination of Fasting Blood Sugar (FBS)

Fasting blood sugar (FBS) was determined in serum samples of all studied groups according to (Pilegy, et.al 1962)⁽¹⁶⁾ and (Trinder, 1969) methods⁽¹⁷⁾

Determination of Glycated Haemoglobin (HbA_{1c})

Glycated Haemoglobin (HbA_{1c}) was determined in whole blood samples of all studied groups according to (variant hemoglobin A_{1c} program (1997))⁽¹⁸⁾

Determination of total proteins (TP).

Total proteins were determined in serum samples of all studied groups according to biuret method.⁽¹⁹⁾

Determination of serum albumin

Albumin level was determined in serum samples of all studied groups according to (Dumas, et.al 1977) method⁽²⁰⁾

Determination of Erythrocytes Sedimentation Rate (ESR)

Erythrocytes Sedimentation Rate (ESR) was determined in whole blood samples of all studied groups according to (Bick, 1993) method⁽²¹⁾

Determination of C-reactive protein (CRP)

CRP was measured in serum samples of all studied groups according to (Ward & Cooper, 1975)⁽²²⁾ and (Young 1995) methods⁽²³⁾

Determination of Immunoglobulin α_1 -antitrypsin

α_1 -antitrypsin was determined in serum samples of all studied groups according to (Fahay & McKelevey, 1965)⁽²⁴⁾ and (Berne (1974)⁽²⁵⁾ methods.

Statistical analysis: Data presented were the means and standard deviations, student -t- test was used to compare the significance of the difference in the mean values of any two groups. ($P \leq 0.05$) was considered statistically significant⁽²⁶⁾.

The overall predictive values for the results in all studied groups were performed according to program of office XP 2002.

Results and Discussion

Table (1) and (2) and figures (1) and (2) showed the levels of F.B.S and HbA_{1c} in sera of patients with type 1 (IDDM), type 2 (NIDDM) and control.

A marked increase in F.B.S (8.3 ± 3.08 , 13.3 ± 1.970) and HbA_{1c} (7 ± 0.62 , 10 ± 1.416) levels in sera of type 1 and type 2 compared to control (4.23 ± 0.93 , 5.27 ± 0.726) respectively was found. All elevated levels were significant between both patients groups and control also between the groups themselves for F.B.S and HbA_{1c}.

A healthy person has around 20,000 insulin receptors sites per cell, while people with insulin resistance can have as low as 5000 of these sites per cell, the result of this is that glucose

can not be efficiently transferred by insulin through these receptor sites from the blood stream into the cell to be burned as energy This causes elevated blood sugar level⁽²⁷⁾ Two factors determine the glycosylated hemoglobin levels: the average glucose concentration and the red blood cell life span if the red blood cell life span is decreased because of another disease state such as hemoglobinopathies, the hemoglobin will have less time to become glycosylated and the glycosylated hemoglobin level will be lower ⁽¹⁵⁾ because A1c based on hemoglobin both qualitative and quantitative variations in hemoglobin can effect the A1c value ⁽²⁸⁾.

Some researches demonstrated the relationship between iron and glucose metabolism, because iron modulates insulin action in human ⁽²⁹⁻³¹⁾.

Table (1): F.B.S level in sera of three studied groups

GROUPS	NO.	F.B.S (mmol/L) Mean $\pm$ SD	P
Control	50	4.2 $\pm$ 0.93	
Type 1	50	8.3 $\pm$ 3.08	P $\leq$ 0.05
Type 2	50	13.3 $\pm$ 1.97	P $\leq$ 0.05
			*P $\leq$ 0.05

P* = P .Value between Type1 and Type2

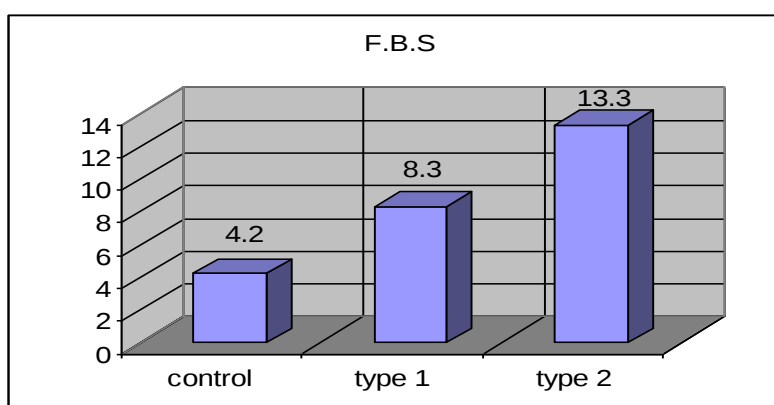


Figure (1): F.B.S level in sera of three studied groups

Table (2): HbA_{1c}% in sera of three studied group

GROUPS	NO.	HbA1c% Mean $\pm$ SD	P
Control	50	5 $\pm$ 0.72	
Type 1	50	7 $\pm$ 0.62	$P \leq 0.05$
Type 2	50	10 $\pm$ 1.41	$P \leq 0.05$
			* $P \leq 0.05$

P* = P .Value between Type1 and Type2

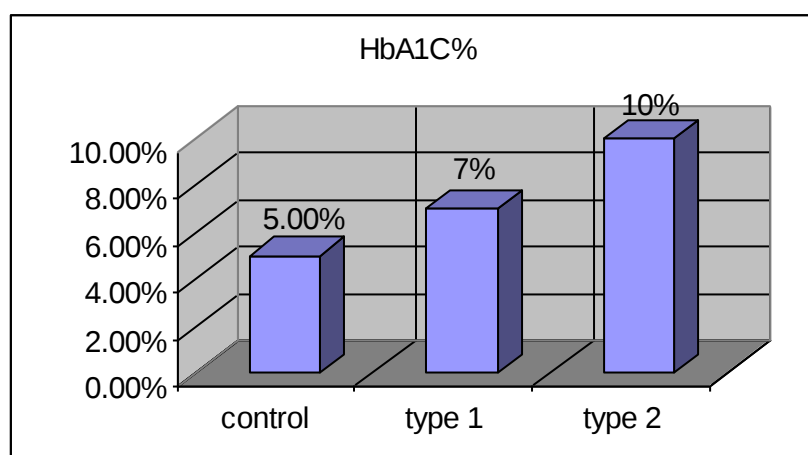


Figure (2): HbA_{1C}% in sera of three studied groups

Table (3) and figure (3) show the results of total protein (TP) in (g/dL) and albumin in (g/dL) in sera of type 1 (IDDM), type 2 (NIDDM), and control group. Total protein and albumin for control group is (6.88 $\pm$ 0.77) (4.83 $\pm$ 0.009), for type 1 group is (6.85 $\pm$ 0.651) (4.760 $\pm$ 0.227) g/do, and for type 2 group is (6.99 $\pm$ 0.716) (3.43 $\pm$ 0.177) g/dL respectively.

From the table (3) there was no significant difference in total protein levels between group type1 and group of control, with P value equal (0.856) which is high than (0.05) as ($P \leq 0.05$) is considered significant, no significant difference between control and type 2 group P value equal (0.462) also no significant differences between both groups of patient type 1 and type 2 with P value equal (0.323).

A significant reduction of albumin level for type 2 group. Compared to control with P value (7.43 $\times 10^{-76}$) while no alteration in albumin level between type 1 and control groups was

found. Also significant differences were found between type 1 and type 2 with P value (2.77×10^{-54}). Albumin normally makes the largest single contribution to plasma total protein.

Total protein levels may be misleading, and may be normal in the face of quite marked changes in the constituent proteins. For example: A fall in albumin may roughly be balanced by arise in immunoglobulin levels. This is quite a common combination. Most individual proteins, other than albumin, make a relatively small contribution to total protein; quite a large percentage change in the concentration of one of them may not be detectable as a change in total protein ⁽³²⁾. Constituent proteins, only low albumin levels are of a clinical importance ⁽³³⁾. A low plasma albumin level despite a normal total body albumin may be due to dilution by an excess of protein – free fluid, or to redistribution into the interstitial fluid due to increased capillary permeability. There may be true albumin deficiency due to a decreased rate of synthesis, or to an increased rate of catabolism or loss from the body.

The slight fall in the albumin level found in even mild acute illness may be due to a combination of the above two factors ⁽³⁴⁾.

Reduction in albumin concentration was reported in inflammatory processes, including acute-phase response and chronic inflammatory disorders and in neoplastic diseases ⁽³⁵⁾

Table (3) TP and Albumin levels in sera of three studied groups

GROUPS	NO.	TP(g/dl) Mean ± SD	p	Albumin (g/dl) Mean ± SD	P
Control	50	6.88 ±0.77		4.83 ±0.009	
Type 1	50	6.85 ±0.65	P>0.05	4.76 ±0.22	P>0.05
Type 2	50	6.99 ±0.71	P>0.05	3.43±7.43	P≤0.05
			*P>0.05		*P≤0.05

P* = P .Value between Type1 and Type2

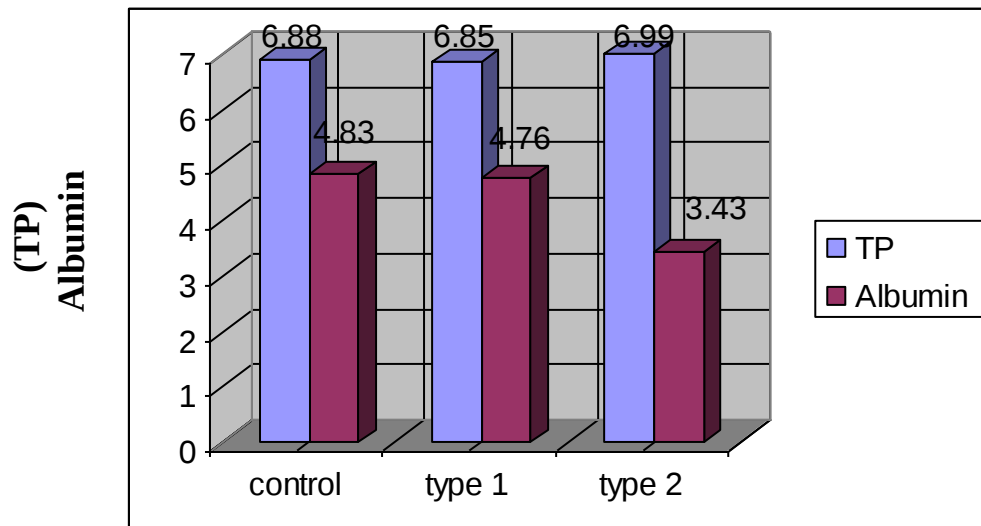


Figure (3) TP and Albumin levels in sera of three studied groups

Table (4) and figure (4),(5),(6) showed the results of ESR, CRP and α_1 -antitrypsin in sera of patients with type 1 type 2 DM and control groups.

A significant increase in level of ESR, CRP, α_1 -antitrypsin levels in sera of patients with type 2 DM compared with control($P \leq 0.05$), while no significant alteration in ESR, CRP, α_1 -antitrypsin levels in sera of patients with type 1 DM compared with control, also a significant differences was found between both patients groups themselves.

Under physiologic conditions the liver synthesizes mainly constitutive hepatic proteins, such as albumin, prealbumin, or transferrin. After trauma the synthesis shifts from constitutive-hepatic proteins to acute phase proteins, such as haptoglobin, α_2 -macroglobulin, α_1 -acidglycoprotein, and C - reactive protein (CRP)⁽³⁶⁾.

This reaction of the liver is called the hepatic acute phase-response. The goal of the hepatic acute-phase response is to restore homeostasis, however, a prolonged and exaggerated response leads to the enhancement of hypermetabolism and catabolism, thus to increase morbidity and mortality⁽³⁷⁻³⁹⁾.

Mediators of the acute-phase-response are pro-inflammatory cytokines, such as interleukin-1 (IL-1B), inter leukin-6 (IL-6), interlukin-8 (IL-8), tumor-necrosis factor (TNF), or the anti-inflammatory cytokine interleukin -10 (IL-10)⁽⁴⁰⁾.

An inflammatory pattern indicating an inflammatory condition is seen when there is a decrease in albumin and an increase in the α_1 -globulins (α_1 -acid glycoprotein, α_1 -antitrypsin), α_2 -globulis (Ceruloplasmin and haptoglobin), and β -globulin blood (C-Reactive protein)⁽¹⁵⁾ Although the main physiological abnormalities are insulin resistance and impaired insulin

secretion⁽⁴¹⁾, specific underlying determinates of these metabolic defects remain uncertain. An accumulating body of evidence suggests that inflammation may play a crucial intermediary role in pathogenesis, thereby linking diabetes with a number of commonly coexisting conditions thought to originate through inflammatory mechanisms⁽⁴²⁾.

Inflammation as measured by C - reactive protein (CRP) has been shown to be increased in people with type 1 and type 2 diabetes that have macro vascular complications⁽⁴³⁾⁽⁴⁴⁾

Increased serum levels of inflammatory biomarkers of arteriosclerosis, like c-reactive protein, cytokins, like tumor necrosis factor-alpha or interleukin-6, as well as novel markers like monocyte chemoattractant protein (MCP)-1, soluble CD40 ligand (sCD40L), and matrix metalloproteinases (MMP) have been shown to predict cardiovascular risk and seen to reflect the over all burden of vascular disease in patients⁽⁴⁵⁾.

Our results agree with studies claimed that some of these markers are elevated in patients with type 2 diabetes and insulin resistance, indicating a pivotal role of inflammation in this metabolic disorder⁽⁴⁶⁾⁽⁴⁷⁾. However, the results of present study agree with previous study found a positive correlation between inflammatory markers and type 2 diabetes⁽⁴⁸⁾⁽⁴⁹⁾.

The research data suggest that the release of inflammatory mediators like tumor necrosis factor-alpha and interleukin -6 (IL-6) from the visceral adipose tissue as well as an activation of vascular cells itself contribute to the inflammatory state in these patients with metabolic syndrome⁽⁵⁰⁾.

Adipose tissue (body fat) has been lately regarded as a separate body organ which can produce a number of different biologically active molecules-such as cytokine proteins that are associated with inflammation, and the hormone resistance, which is linked to insulin resistance and the development of type two diabetes⁽⁵¹⁾.

(Jerome and Rotter)⁽⁵²⁾ Showed that four specific gene variations were significantly linked with high levels of insulin resistance. Among these inflammatory genes, IL4, IL 4R and C4 were found to have significant variation despite the patients age, sex, or body mass index (BMI), while variation in IL6 affected insulin resistance only through excess body fat "Rotter said" in other words, it appears that low grade inflammation causes insulin resistance and is not just a consequence of insulin resistance.

There is now evidence that insulin improves hyper metabolism by affecting pro-inflammatory cytokine production and hepatic signal transcription factor expression⁽⁵³⁾.

In the present study we investigated the effects of insulin hormone and daonil drug on the systemic inflammatory response in patients with type 1 and type 2 DM respectively both suffering from the same inflammatory diseases. Without taking any non steroidal anti inflammatory, aspirin and statin drugs, ACEI, and Glitazones. Showed that insulin is decreasing pro-inflammatory hepatic acute-phase protein concentrations in sera of patients with type 1 DM group compared with the effects of daonil drug on the systemic inflammatory response in patients with type 2 DM.

Results given the fact that the insulin treat diabetes also may have potential treatment for inflammatory diseases.

These data suggest that insulin acts as an anti-inflammatory molecule through direct cellular effects rather than through indirect effects, which would be by modulating glucose concentration.

Insulin at a dose that kept blood glucose below 110mg/dL decreased mortality and prevented the incidence of multi-organ failure in critically ill patients⁽⁵⁴⁾.

In an animal model, insulin had anti-inflammatory effects by decreasing pro-inflammatory signal transcription factors and pro-inflammatory cytokines, while increasing anti-inflammatory cytokines. However, it is still unknown whether insulin exerts its effects directly through modulating pro-inflammatory mediators or indirectly through modulating glucose concentration⁽⁵³⁾.

Table (3-4) ESR, CRP, Alpha₁- antitrypsin levels in sera of three studied groups

GROUPS	No.	ESR(mm/1hr) Mean ± SD	P	CRP(mg/dl) Mean ± SD	Alph 1 – antitrypsin(mg/dl) Mean ± SD	P
Control	50	10.4 ±3.79		-	131.1± 45.3	
Type 1	50	12.5 ±3.78	P≤0.05	-	130.4±32.8	P>0.05
Type 2	50	32.4±8.67	P≤0.05	9 ±0.302	194±4.6	P≤0.05
			*P≤0.05			*P≤0.05

P* = P .Value between Type1 and Type2

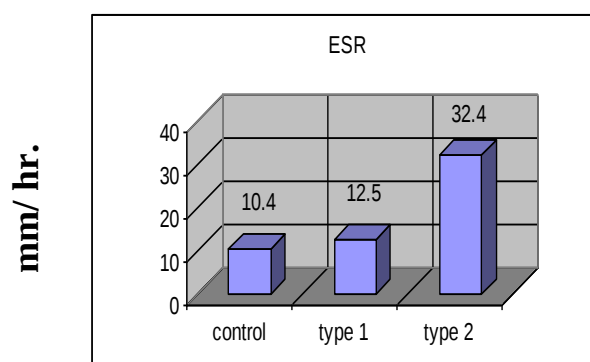


Figure (4) ESR level in three studied groups

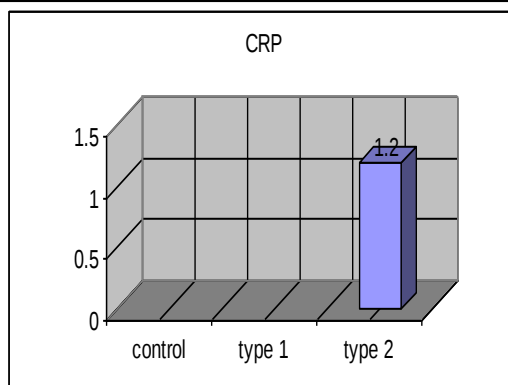


Figure (5) CRP level in sera of three studied groups

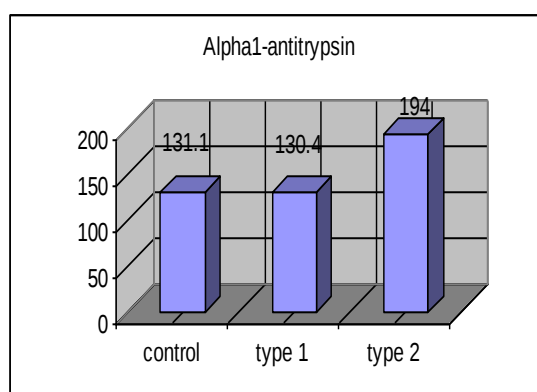


Figure (6) Alpha₁- antitrypsin level in sera of three studied groups

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تأثير الانسولين على الاستجابة الالتهابية مقارنة بالسلفونيل يوريا في مرضى داء السكري
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الخلاصة

صُمِّمَتْ هذه الدراسة لتكون الحجر الاساس لدور الأنسولين كعامل مضاد للالتهاب في
عمليات الإلتهاب المختلفة.

أخذت نماذج عينات الدم الوريدية للصائمين من ١٥٠ فردا و التي منها ٥٠ مريض بنوع
مرض السكر ١ ، ٥٠ مريض بنوع مرض السكر ٢ ، و ٥٠ فرد من الاصحاء.
حللت كل نماذج الدم لقياس سكر دم الصائم و النسبة المئوية للهيموغلوبين المسكر والبروتين
الكلبي و الالبومين ومعدل ترسيب كريات الدم الحمراء وبروتين س-التفاعلي والفا -١-مضاد
للتريسين .

بينت نتائج الدراسة الحالية زيادة في معدل سكر دم الصائم والنسبة المئوية للهيموغلوبين
المسكر ، في كُلٍّ من مرضى النوع الاول والثاني مُقارنة للسيطرة.
كانت مستويات البروتين الكلبي بدون تغيير في مصل دم كلتا مجاميع المرضى مقارنة
بالسيطرة.

وجد نقصان في مستوى الالبومين في مصل مرضى النوع ٢ مقارنة لمجاميع مرضى النوع
١ او السيطرة.

ارتفعت عوامل التشخيص لاي نوع من العملية الالتهابية معدل ترسيب كريات الدم الحمراء
وبروتين س-التفاعلي والفا -١- مضاد للتريسين عند مرضى نوع ٢ مقارنة لمجاميع
مرضى نوع ١ والسيطرة

مفتاح الكلمات

داء السكري ، الانسولين ، سلفونيل يوريا ، بروتينات الطور الحاد