Comparison between tight and moderate glycemic control in diabetic patients undergoing coronary artery bypass grafting

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Abstract:

Background: The dynamic glycemic control of diabetic patients undergoing coronary artery bypass graft operation by insulin is very important. The insulin has immunoregulatory effects and expected to decrease the formation of CRP and proinflammatory cytokines such as IL-6, TNF-α, ICAM-1, and E-selectin by inhibition of their transcription. The study compared between hazards and benefits of both tight and moderate glycemic control for these patients.

Methods: Data obtained in 60 diabetic patients with normal left ventricular function arranged for elective coronary artery bypass surgery, who were randomly distributed into two groups, tight (blood glucose 80-120 mg/dl) and moderate (blood glucose 120-180 mg/dl) glycemic group. Regular insulin was infused at a specific rate for each group. Systemic inflammatory response (IL-6 and CRP plasma levels), blood glucose levels, number of blood sugar measurements within target value, hypoglycemia incidence, the inotropic support need and its duration, the ventilatory support duration, surgical wound infection incidence, renal impairment and the need for renal replacement therapy were measured.

Results: Comparing between the systemic inflammatory response in the tight and moderate group (group I and group II respectively), there was higher statistically significance in plasma level of pro-inflammatory cytokine IL-6 in group I (P=0.001). Also, there was higher statistically significance in plasma level of C - reactive protein (CRP) in group I (P=0.001). There was a statistically significant difference regarding the duration of inotropic support use (median value of the number of hours) in group I and group II. The duration of use of inotropic support was significantly higher in

group I (P=0.002). There was no statistically significant difference between two groups regarding the other measurements.

Conclusion: The moderate glycemic control in diabetic patients undergoing CABG is not inferior to tight glycemic control but it achieved better results as it had less inflammatory response, less inotropic support time and avoiding aggressive hypoglycemia side effects.
Keywords: systemic inflammatory response, CABG, glycemic control, insulin, diabetes, cardiovascular.

Background:

During cardiac surgery especially during cardiopulmonary bypass, perioperative hyperglycemia occurs frequently in patient with and without diabetes [(1)].

Diabetes pathogenesis is not fully understood, but rising evidence contacts diabetes to a chronic inflammation state, which happens in tissues such as liver, adipose, and skeletal muscle and results in inflammatory cytokines release such as IL-6, TNF-α, , IL-1β, IL-8 and resistin from macrophages and/or adipocytes [(2)]. Rises in the plasma and/or tissue concentrations of these cytokines is thought to have a negative effect on metabolism and stimulation of peripheral insulin resistance [(3)].
Increased blood glucose levels is an important risk factor for death, cardiovascular, renal, respiratory, and infectious complications [(3)]. Benefits of decreasing blood glucose are to prevent damage to vital organs and thereby to advance critically ill patients outcome [(4)].

During cardiac surgery, it is difficult to reach and maintain euglycemia due to severe surgical stress. Also, the inflammatory response is markedly complex, and sensitive to the usage of intraoperative CPB and cardiotomy suction. Besides, IL-6 in hepatocytes increase the CRP gene expression [(5)].

The insulin has immunoregulatory effects and expected to decrease the formation of CRP and proinflammatory cytokines such as IL-6, TNF-α, ICAM-1, and E-selectin by inhibition of their transcription [(6)]. But, intraoperative aggressive insulin management could lead to postoperative hypoglycemia when surgical stress recedes [(7)].

Our hypothesis was that insulin could inhibit the systemic inflammatory response and advance myocardial protection.

Aim of the Work:

To know outcomes and safety of both tight and moderate glycemic control in diabetic patients undergoing CABG surgery perioperatively and to compare between them especially regarding inflammatory cytokines.

Patients and Methods: This study was conducted in Fayoum University hospitals, Cairo University hospitals and National Heart Institution. Approval was obtained from the research ethics committee of the anesthesia department of Fayoum University, Cairo University and National Heart Institution and written consent was obtained from all patients. Sixty adult patients of the same age group with diabetes who had undergone on-pump coronary artery bypass grafting were registered in this study.

Emergency CABG, redo CABG, combined CABG and any other cardiac procedure, patients with poor ventricular function (Ejection Fraction < 40% and patients with impaired liver or kidney functions were the exclusion Criteria.

Study groups

The Patients were randomly allocated into two groups, 30 patients each: ***Group (I)*** as the tight glycemic control group (target blood glucose 80-100 mg %) and ***Group (II)*** as the moderate glycemic control group (target blood glucose < 180 mg %)

Preoperative Management of blood glucose:

24 hours prior to surgery, oral hypoglycemic agents were discontinued. Diabetic patients on insulin had their daily dose of insulin held the evening before surgery and a standard subcutaneous insulin sliding scale was begun until the intraoperative insulin infusion protocol was started.

Intraoperative management of blood glucose:

Each study group followed a separate intraoperative insulin infusion protocol (or method) as shown below:

Group I (Tight dynamic glycemic control method):

The patients in this group followed a dynamic protocol of insulin infusion. The goal of this protocol was to keep blood sugar level between 80-120 mg/dL**.**

Blood glucose levels were tested every 30 minutes. The patients received a regular insulin continuous infusion (Actrapid insulin, Novo Nordisk, Copenhagen, Denmark) in 50ml of 0.9 % NaCl) using a syringe pump. The dose was adjusted under strict supervision of a team of anesthetists and ICU nurses assisted by ICU physicians. Serial blood glucose measurements were achieved by ***(Accucheck Go, Roche, Germany)*** glucose meters.

We were following the protocol by ***Ghandi and coworkers*** [(2)] shown in Table (1) [(2)]:

Column 1		Column 2		Column 3	
Serum glucose Level, mg/dL	Insulin infusion Rate, U/h	Serum glucose Level, mg/dL	Insulin infusion Rate, U/h	Serum glucose Level, mg/dL	Insulin infusion Rate, U/h
>400	18	>400	25	>400	30
351-400	16	351-400	22	351-400	27
301-350	14	301-350	20	301-350	24
251-300	12	251-300	18	251-300	21
201-250	10	201-250	15	201-250	18
176-200	8	176-200	12	176-200	15
151-175	6	151-175	9	151-175	12
121-150	4	121-150	7	121-150	9
101-120	2	101-120	4	101-120	6
80-100	1	80-100	2	80-100	3
<80	Off	<80	Off	<80	Off

Column 1: All patients started in column 1 and restarted in this column when glucose level <80 mg/dL.

Column 2: If patient had not reached glucose level range of 80-120 mg/dL within 2 hours after column 1 usage and glucose level has decreased by <50 mg/dL over preceding 1 hours, column 2 was used.

Column 3: Was used if patients had not achieved blood glucose level range of 80-120 mg/dL within 2 hours of using column 2 and glucose level had decreased by <50 mg/dL over preceding 1 hour.

If glucose level was <60 mg/dL, treatment of hypoglycemia protocol had initiated by 50ml of 10% dextrose infusion. Glucose was then monitored every 30 minutes till glucose level was >80 mg/dL. Then dextrose 10% was discontinued and insulin infusion was always resumed in column 1.

Group II (The moderate glycemic control):

Group II received the intravenous insulin infusion titrated to maintain blood glucose level from 120 - 180 mg/dL. Preparation of this insulin infusion was the same as in group I and blood glucose measurements were also performed by ***Accucheck Go, Roche, Germany*** glucose meters.

The regimen was applied as follows:

- If baseline blood glucose level > 180 mg/dL, a bolus of 2 units was started followed by insulin infusion at 2 units/ hours. Blood glucose measurement was done every 30 minutes.

The regimen is demonstrated in table (2) below:

Table (2): moderate glycemic control regimen

> 180 mg/dl	Increase infusion by 2 units/hour
Between 108 and 180 mg/Dl	Maintain current infusion rate
< 108 mg/dL	Stop insulin infusion
< 72 mg/dL	Stop insulin infusion and administer 25 mL of Dextrose 50%

Maximum insulin infusion = 20 unit per hour [8].

Postoperative management of blood glucose

In the ICU, the tight glycemic control protocol was continued at least 24 hours postoperatively for both study groups until enteral feeding was started. The insulin

infusion was prepared and checked as was stated above. Then diabetic patient restarted their preoperative insulin regimen of oral hypoglycemic [(2)].

Measurements

Blood glucose levels, number of blood sugar measurements within target value, hypoglycemia incidence, the inotropic support need and its duration, the ventilatory support duration, surgical wound infection incidence, systemic inflammatory response (IL-6 and CRP), renal impairment and the need for renal replacement therapy were measured. Renal impairment is defined as increase in serum creatinine by more than or equal to 0.3mg/dL.

IL-6 Assay: Citrated 4.5-mL blood samples were drawn during and after CPB. These were immediately centrifuged (3500*g*, 10 minutes), and plasma was separated and frozen at 220°C until analysis. IL-6 concentrations were measured by using a standard commercial assay (R&D Systems) by a staff blinded to all subject data. Interassay and intra-assay coefficients of variation were 5% and 3%, respectively.

Anesthetic Management:

In the operating room all patients were monitored with 5-lead ECG, pulse oximetry, capnography and nasopharyngeal temperature via Hewlett Packard Merlin Multi-parameter Monitor ***(hp-Merlin).*** After insertion of a peripheral venous line using an 18-gauge cannula preoperative sedation was established with 1 to 3 mg of midazolam. Then the non- dominant hand radial artery was cannulated percutaneously after local anesthetic infiltration of lidocaine 1% as a local anesthetic, using intra-arterial catheter *(Abbocath-T 20gauge)* for direct arterial blood gas monitoring and invasive blood pressure measurement. This was done after performing Allen's test. All patients received prophylactic perioperative antibiotics (Cefoperazone 1 g pre-incision and 1 g post-CPB, or vancomycin 1 g pre-incision and 500 mg post-CPB if allergic to penicillin).

Anesthetic induction

All patients were preoxygenated with 100% oxygen for 3-5 minutes using a face mask. Then anesthesia was induced by using fentanyl (3-10µg/kg), midazolam (0.1mg/kg), thiopental sodium "sleeping dose" (1mg/kg) and pancuronium bromide (0.1mg/kg) and all the drugs were titrated to the patients response, and the patients were ventilated for 3-5 minutes using a face mask until complete relaxation, then an 8-sized oral cuffed endotracheal tube in male patients and 7-sized endotracheal tube in female patients was inserted by direct laryngoscopy and the patients were mechanically ventilated.

Maintenance of anesthesia

The patients were mechanically ventilated using (Datex-Ohmeda excel 210 machine) with a tidal volume of 7-10 ml /kg and a respiratory rate of 10-12 breathes per minute. Anesthesia was maintained by isoflurane (0.5%-1.5 volume %). fentanyl (up to a total of 25 µg/kg according to the hemodynamic data. Pancuronium 0.02 mg/kg top up doses were given every 45 minutes.

Patients were monitored by continuous ECG, pulse oximetry, capnography, direct arterial blood pressure tracing, and frequent blood gases and electrolyte measurements to ensure efficient ventilation and acid-base balance.

Cardiopulmonary bypass

Immediately prior to CPB, heparin 300 IU/Kg was intravenously administered followed by additional doses, if necessary, to maintain an activated clotting time (ACT) greater than 500 seconds. Cardiopulmonary bypass was conducted by cannulation of the ascending aorta and a single double-staged right atrial cannulation. A cobe membrane lung oxygenator was used for blood oxygenation with a roller pump with non-pulsatile flow of 2.2-2.5L/min/m^2. The circuit was primed with 1500 ml balanced salt solution and 150ml mannitol. The temperature was allowed to drift to 32^{o}C.

In the ICU: All the patients were monitored using the same standard monitoring namely 5-lead ECG, pulse oximetry, capnography, and nasopharyngeal temperature using the Hewlett Packard Merlin Multi-Parameter Monitor ***(hp-Merlin).*** Also, as has been previously mentioned, all patients followed the tight glycemic control regimen postoperatively until enteral feeding was started.

Statistical Analysis: Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test, paired t-test, Chi-square, Linear Correlation Coefficient and Analysis of variance [ANOVA] tests by SPSS V17. Unpaired Student T-test was used to compare between two groups in quantitative data.

Results:

Between April 2012 and December 2014, a total of 60 participants were recruited to this study and were randomly allocated to group I (30 participants) or group II (30 participants). The results revealed no significant changes between both groups regarding demographic characteristics as shown in Table (1).

Tab 1: Demonstration data in both groups

Demonstration data		Group I (N=50)	Group II (N=50)	P value
Age		53.700 ± 5.342	54.060 ± 4.838	0.72
Gender	Male	21 (76%)	19 (74%)	1.00
	Female	9 (24%)	11 (26%)	
Weight		86 ± 13.67	81 ± 9.20	0.71
BMI		33.5 ± 7.08	29.66 ± 5.32	0.67

Comparing between the systemic inflammatory response in the tight and moderate group (group I and group II respectively), there was higher statistically significance in plasma level of pro-inflammatory cytokine IL-6 in group I (P=0.001) as shown in figure 1. Also, there was higher statistically significance in plasma level of C - reactive protein (CRP) in group I (P=0.001) as shown in figure 2.

Figure (1): Primary outcome; IL-6 in both groups:

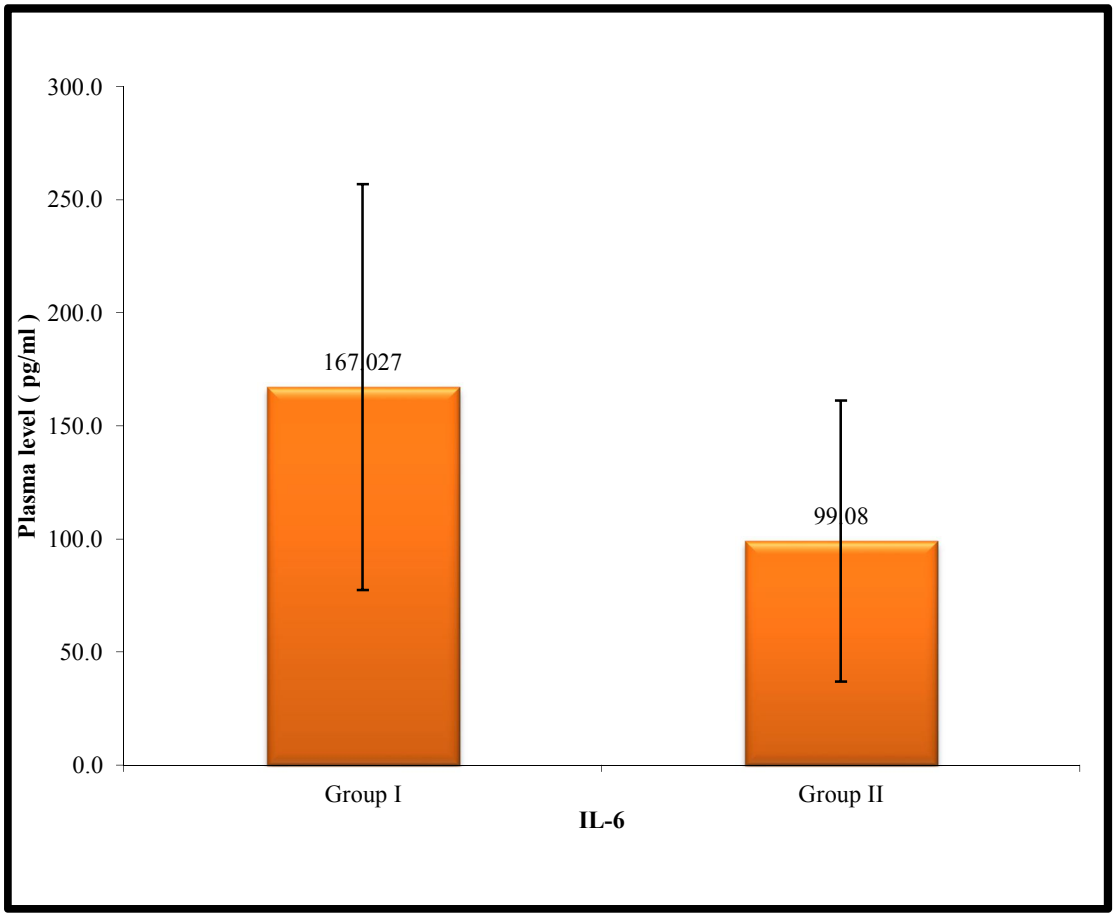
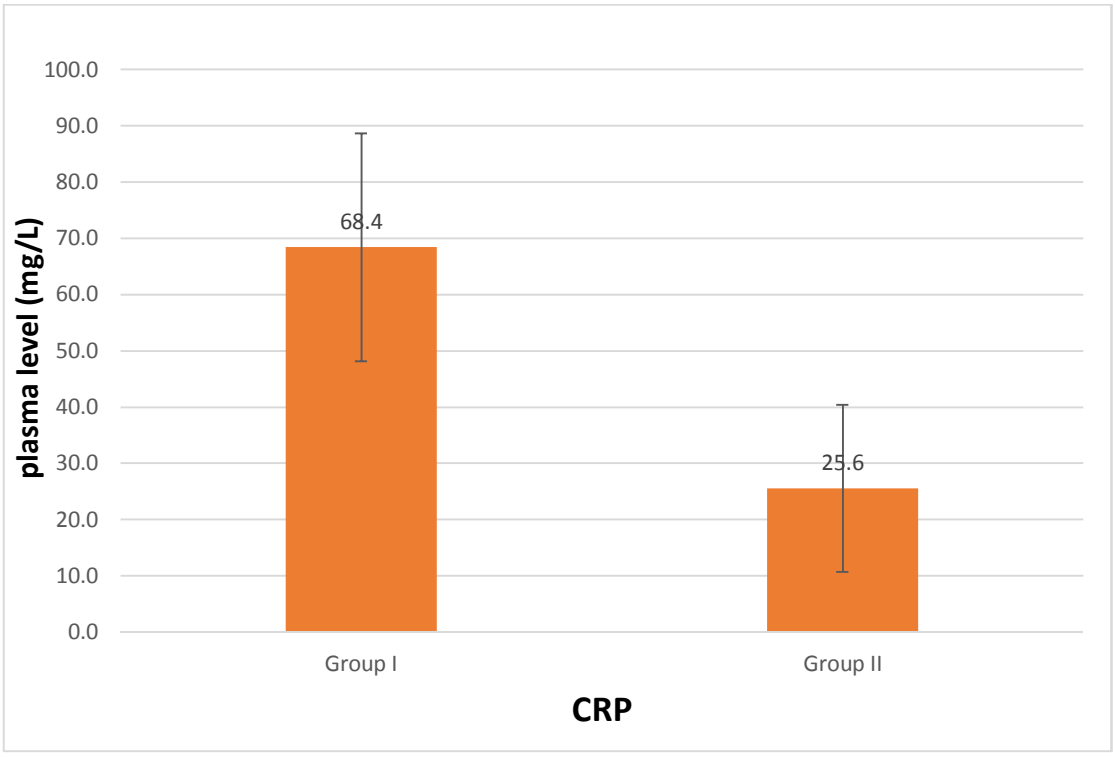


Figure (2): C - reactive protein (CRP) in both groups:



There was a statistically significant difference regarding the duration of inotropic support use (median value of the number of hours) in group I and group II. The duration of use of inotropic support was significantly higher in group I (P=0.002).

There was no statistically significant difference between two groups regarding number of measurements of blood sugar within target value, incidence of hypoglycemia, need of inotropic support, duration of ventilation, renal impairment and wound infection.

Tab 2: Secondary outcomes in both groups:

Secondary outcomes	Group I (N=50)	Group II (N=50)	P value
Number of measurements of blood sugar within target value	78.180 ± 11.317	82.000 ± 13.406	0.1296
Incidence of Hypoglycemia	5 (16.66%)	1 (3.33%)	0.084
Need of inotropic support	28 (93.33%)	27 (90.00%)	0.640
Duration of Inotropic support	11.20 ± 4.21	7.26 ± 3.45	0.002*
Duration of ventilation	8.600 ± 2.231	9.720 ± 3.676	0.069
Renal impairment	1 (3.33%)	1 (3.33%)	1.000
Wound infection	1 (3.33%)	1 (3.33%)	1.000
Intraoperative mortality	None	None	---

Discussion:

Our study proved that moderate glycemic control is better than tight glycemic control for diabetic patients undergoing CABG operation.

Similar to our study, many studies on cardiac surgical diabetic patients classified the patients into two groups, tight and moderate glycemic control groups like Thomas [(9)], Lazar HL [(10)] and Gandhi and coworkers [(2)].

In our study, according to the glycemic control protocol, the insulin was infused continually intraoperatively. Postoperative plasma concentrations of IL-6 and CRP were measured on the day of surgery.

Thomas and coworkers study [(9)] demonstrated that their results support their prior findings and indicate that a moderate glycemic control strategy during coronary artery bypass leads to enhancements in health-related quality of life and survival rates that are similar to those reached with a severe target range. In addition, the liberal strategy has superiority in glucose control and target range management.

Regarding the safety of glycemic control, statistically significant more incidences of hypoglycemia were observed in the tight glycemic group (4 patients) 14% versus (1 patient) 3% in the moderate group in our study. Azam and coworkers [(3)] in their study exposed that hypoglycemia can also be harmful because the brain is an obligate glucose metabolizer. Severe hypoglycemia leads to neuronal necrosis via increased excitatory amino acids concentrations, with more affection of the superficial layers of the cortex and the dentate gyrus of the hippocampus; however, the cerebellum and brainstem are spared injury. Low BG levels also cause increased glucagon, epinephrine, growth hormone, and cortisol secretion. In diabetic patients, hypoglycemia is associated with neurogenic and neuroglycopenic symptoms including: seizure, coma, or even death.

In our study, we demonstrated that maintenance of blood glucose in a moderate glycemic control perioperatively in CABG in diabetic patients with CBP led to perioperative outcomes similar to those achieved with a strict target range and was superior in glucose control, target range management, less duration of inotropic support and suppressed inflammatory response.

Our study matched with Castigliano and coworkers [11], Griesdale and coworkers [12] and Lazar and coworkers [6] as they found that moderate glycemic control was superior to tight glycemic control, with decreased mortality and major complications, and may be ideal for patients undergoing isolated coronary artery bypass grafting.

In our study, regarding the need of inotropic support, there were no statistically significant differences between group I and group II regarding the need of inotropic support. But the moderate glycemic control has statistically significant reduction in the duration of inotropic support use (being < 12 hours or > 12 hours) in group II versus group I (P = 0.022).

As some studies demonstrate while others fail to prove that insulin decreases the need of inotropic support, we have found no studies on the insulin effect on the duration of inotropic support use. Our study proved that insulin had no outcome on the need but decreased the duration of inotropic support use. We need to conduct further studies aiming to discover and explicate how insulin may affect the duration of inotropic support use in CABG patients.

As regards the duration of ventilation there was no statistically significant between group I and group II.

Desai et al [13] study demonstrated that the moderate group was also superior to the tight group in the perioperative results of prolonged ventilation, pneumonia, deep sternal wound infection, perioperative renal failure, and operative mortality. On the basis of these results, it seems reasonable to set the target BG range to between 121 and 180 mg/dL for this group of patients undergoing first-time isolated CABG.

On the other hand, the study by Gandhi and coworkers [2] demonstrated that there was no difference in the incidence of prolonged ventilation 19% in TGC group versus 20% in conventional group (P = 0.82).

Diabetic patients have an advanced inflammatory response that can lead to the postoperative capillary leak syndrome, which results in increased lung water accumulation and altered autonomic tone. These patients have increased fluid collection and need ventilatory support for longer periods [14].

Our study may presume that perhaps higher doses of insulin usage may incompletely counteract these harmful effects of insulin deficiency and/or resistance on the lung. Also it suppose that the insulin inotropic and vasodilator effects may decrease lung congestion.

In our study there was no statistically significant difference between the incidence of renal impairment in both groups (P=1.000). Only one case of renal impairment occurred in group I (TGC) and also one case of renal impairment occurred in group II. The study by De la Rosa and coworkers [(15)] was similar to our results but against our results was the study by Van den Berghe and coworkers [(16)].

As regards wound infection in our study , the tight glycemic control group showed one case incidence of wound infection and also the moderate group showed one case incidence of wound infection (p=1.000).

With regard to the systemic inflammatory responses, our study proved a decrease of inflammation with the 2 groups but there was major reduction of inflammatory cytokine mediators such as IL-6 and CRP in the moderate glycemic control group.

Comparing between the systemic inflammatory response in the tight and moderate groups, there was higher statistically significance in plasma proinflammatory cytokine IL-6 level in group I (P=0.001). Also, there was higher statistically significance in plasma level of CRP in group I (P=0.001).

Our results agreed with Desai et al, [(13)] study results as they found significant decrease in inflammatory mediators as IL-6, CRP and ESR in moderate glycemic control.

Against our study, Lazar et al, [(6)] had shown in their series that one of the aggressive glycemic control benefits is that inflammation markers, such as free fatty acids, are markedly reduced.

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