Glycemic Control, Coagulation and Fibrinolytic Response to Weight Loss in Obese Non-insulin Dependent Diabetic Patients

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Abstract: Background: Obesity must be considered as a disease in its own right but is also a risk factor for other diseases, as a result of overweight and the frequently associated metabolic disorders, also a variety of defects in platelet function has been identified in human obesity. Objective: The purpose of this study was to investigate the effect of weight reduction on Glycemic Control, the fibrinolytic and coagulative factors in obese non-insulin dependent diabetic patients. Material and Methods: Sixty obese non-insulin dependent diabetic patients with body mass index (BMI) ranged from 30 to 35 Kg/m², their age ranged from 35 to 50 years were included into this study and divided into two equal groups. The first group (A) received physical training combined with dietary measures and medical treatment. The second group (B) received only medical treatment and no physical therapy intervention. The program consisted of three sessions per week for three months. Glycated hemoglobin (HbA1c), Coagulation and fibrinolytic factors were assessed both before and after treatment program in both groups. Results: There was a significant reduction in HbA1c, BMI, Fibrinogen, von Willbrand factor (vWF-Ag) antigen, plasminogen activator inhibitor-1 activity (PAI-1:Ac) and antigen (PAI-1:Ag) & increase in prothrombin time (PT), partial thromboplastin time (PTT), tissue plasminogen activator activity (tPA:Ac) and antigen (tPA:Ag) in group (A) after training. However, there was a significant differences between both groups (P<.05).Conclusion: The results of the current study revealed that Glycemic control, coagulation and fibrinolytic activity could be improved by weight reduction in obese non-insulin dependent diabetic patients.

Key words: Glycemic control, Diabetes, Fibrinolysis; Coagulation; Weight Reduction; Obesity.

INTRODUCTION

Obesity is often associated with serious medical problems, such as premature atherosclerosis, and imparts a high risk of mortality from cardiovascular disease (CVD) due to atherothrombotic events (Després, JP., 2007). Obesity independently increases the risk of developing diabetes 10-fold compared with that for patients who are normal weight (Després, JP., 2007). Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (American Diabetes Association, 2005). Abnormalities of platelet function–together with activated coagulation, hypofibrinolysis and endothelial dysfunction–result in an elevated thrombotic tendency and play a major role in the increased prevalence of cardiovascular events among the patients with obesity and insulin resistance (Alessi, MC, 2003).

Platelet hyperactivation is an early event occurs in obese subjects independently of the appearance of hyperglycemia and can be explained, at least in part, by a reduced sensitivity to the antiaggregating agents and modulate platelet responses in physiological conditions (Moreno, PR, 2004; Trovati, M, Anfossi, G., 2002). Several studies have demonstrated that increased plasma levels of plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (t-PA) are independent predictors of CVD and that these parameters are implicated in the development of atherothrombosis in this population (Alberti, KG, et al., 2005; Mertens, I, Van Gaal, LF., 2002).

Low caloric diets are effective in improving glycemic control and blood lipids through weight loss in overweight non insulin dependent diabetes mellitus patients (Harder, H., et al., 2004). Also, exercise training has been suggested to improve glucose tolerance and insulin action in patients with type 2 diabetes. However, it is not really known how much exercise is required to achieve this effect. Although there have been many studies on the effect of exercise in patients with type 2 diabetes, their results have varied (Glans, F., et al., 2009).
Diet is one of many variables, which may modify coagulation and fibrinolysis. Variations in the amount and type of fat in the diet have been shown to alter Factor VIIc (Miller, G.J., 1986) fibrinogen (Oosthuizen, W, et al., 1994) tissue plasminogen and plasminogen activator inhibitor type-1 concentrations and/or activities (Emeis JJ, et al., 1989). However, Regular physical activity, one of the mechanisms mediating the cardioprotective effect may be changes in the hemostatic system, particularly fibrinolysis and coagulation (DeSouza, CA., et al., 1979; Stevenson, ET, et al., 1995; Rankinen, T., 1993). Cross-sectional studies report greater fibrinolytic activity in physically active as compared with inactive individuals (DeSouza, CA, et al., 1998; Szymanski, LM, et al., 1994).

The purpose of this study was to investigate the effect of weight reduction on Glycemic Control, the fibrinolytic and coagulative factors in obese non-insulin dependent diabetic patients.

MATERIAL AND METHODS

Subjects:
Sixty obese non-insulin dependent diabetic patients of both sexes with total body obesity (body mass index (BMI) ranged from 30 to 35 Kg/m², free from respiratory, kidney, liver and neurological disorders. Their age ranged from 35 to 50 years. The subjects were included into 2 equal groups; group (A) received medical treatment, physical training combined with dietary measures. The second group (B) received only medical treatment, asked to maintain their ordinary life style and received no physical therapy intervention. Exclusion criteria included: smoking; any prescribed medications, including regular aspirin, nonsteroidal anti-inflammatory drugs, hypertension, diabetes, personal history of CVD, thyroid disease and orthopedic problems inhibiting treadmill training. Informed consent was obtained from all participants. All participants were free to withdraw from the study at any time. If any adverse effects had occurred, the experiment would have been stopped, with this being announced to the Human Subjects Review Board. However, no adverse effects occurred, and so the data of all the participants were available for analysis.

Methods:
Evaluated Parameters:

Chemical Analysis:
Blood samples were collected from the antecubital vein at the beginning and end of the treatment program. After a 12 h fast, subjects had blood drawn at the same time in the morning on each occasion (between 8 and 10 AM). Subjects lay supine for 10 min prior to the blood collection. 10 mL of blood was drawn into a tube containing 0.1 M sodium citrate. Blood was centrifuged at 2000 ×g for 10 min at 4 °C and stored at −80 °C until analysis of glycosylated hemoglobin (HBA1c), coagulation and fibrinolytic factors. Plasma vWF was measured by available commercial Enzyme Linked Immuno Sorbent Assay (ELISA) method (Zymutest vWF, Hyphen Biomed, Neuville sur Oise, France). PT and PTT were determined using (Tromboplastin D, Fisher Diagnostics, Middeltown, USA) and (APTT-XL, Fisher Diagnostics, Middeltown, USA). tPA and PAI-1 activities and antigens were determined using the Imulysite™ enzyme-linked immunosorbent assay (ELISA) kits (Biopool, Umea, Sweden) and the activities using Chromolize™ tPA and Spectrolyse® pL PAI (Biopool, Umea, Sweden) in accordance with the manufacturer’s instructions. All standards and samples were measured in duplicate and all samples from the one subject were measured on the same plate; Fibrinogen was measured by the time titration method employing the ST-4 coagulation instrument (Zymutest Fibrinogen, ELISA, Hyphen Biomed, Neuville sur Oise, France).

B. Evaluation of Anthropometric Parameters:
All measurements were performed at pretreatment and after three months at the end of the study. The participants were measured whilst wearing their undergarments and hospital gowns. Height was measured with a digital stadiometer to the nearest 0.1 cm (JENIX DS 102, Dongsang, South Korea). Body weight was measured on a calibrated balance scale to the nearest 0.1 kg (HC4211, Cas Korea, South Korea), and BMI was calculated as Body weight/Height².

Weight Reduction Methods:
The Prescribed Low Calorie Diet:
The interview-based food survey was performed for all patients by dieticians to specify previous food habits and possible anomalies in dietary behavior. The prescribed low calorie diet was balanced, with 15% as protein, 30 to 35% as fat and 50 to 55% as carbohydrate, on average, in order to provide about 1000 calories daily for two months for whole participants in this study.

The prescribed diet included the breakfast consisted of 2 boiled eggs (80 calorie), 50 gm cheese (100 calorie) and one bread (105 calorie), where the lunch consisted of 2 pieces of boiled meat 100gm (240 calorie),
or chicken (300), 500 gram salad (105 calorie), 300 gram boiled vegetables (110 calorie) 100 gram and banana (100 calorie), However, the dinner consisted of 200 gram light milk (120 calorie).

We checked that food was eaten as three daily meals and we emphasized the need to have a substantial breakfast. The two groups underwent an identical dietary monitoring program, with an initial consultation, a check-up in the middle of the program and another during the final sessions by a dietician who was blinded to the type of the program that the subject had been following.

The Physical Training Program:
The aerobic treadmill-based training program (Enraf Nonium, Model display panel Standard, NR 1475.801, Holand) was set to 65% of the maximum heart rate (HRmax) for one month and increased gradually for 75% of maximal heart rate during the second month of the program achieved according to a modified Bruce protocol. This rate was defined as the training heart rate (THR). After an initial, 5-minute warm-up phase performed on the treadmill at a low load, each endurance training session lasted 30 minutes and ended with 5-minute recovery and relaxation phase. All patients performed three weekly sessions (i.e. a total of 36 sessions per patient over a 3-month period.

Statistical Analysis:
The mean values of BMI, glycated hemoglobin (HBA1c), Fibrinogen, von Willbrand factor (vWF-Ag) antigen, plasminogen activator inhibitor-1 activity (PAI-1:Ac) and antigen (PAI-1:Ag), prothrombin time (PT), partial thromboplastin time (PTT), tissue plasminogen activator activity (tPA:Ac) and antigen (tPA:Ag) obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups (P<0.05).

Results:
There was a significant reduction in HBA1c, BMI, Fibrinogen, von Willbrand factor (vWF-Ag) antigen, plasminogen activator inhibitor-1 activity (PAI-1:Ac) and antigen (PAI-1:Ag) & increase in prothrombin time (PT), partial thromboplastin time (PTT), tissue plasminogen activator activity (tPA:Ac) and antigen (tPA:Ag) in group (A) after training (Table 1 and figure 1). However, changes in group (B) were not significant (Table 2 and figure 2). Moreover, there was a significant difference between both groups (Table 3 and figure 3). (P<0.05).

Table 1: Mean value and significance of the pre and post test values of BMI, PT, PTT, tPA: Ac and tPA: Ag fibrinogen, vWF-Ag, PAI-1: Ac and PAI-1: Ag in the training group.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>t- value</th>
<th>Significant</th>
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<tbody>
<tr>
<td>BMI (Kg / m²)</td>
<td>35.15 ± 5.3</td>
<td>31.14±5.51</td>
<td>5.74</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>PT (s)</td>
<td>10.25 ± 0.56</td>
<td>12.18±0.96</td>
<td>5.52</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>21.71 ± 2.45</td>
<td>25.76±2.91</td>
<td>5.85</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>tPA:Ac (IU/mL)</td>
<td>5.15 ± 0.27</td>
<td>6.5 ± 0.24</td>
<td>4.76</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>tPA:Ag (ng/mL)</td>
<td>3.65 ± 0.71</td>
<td>4.57 ± 0.67</td>
<td>4.73</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Fibrinogen (mg/mL)</td>
<td>3.93 ± 0.66</td>
<td>2.26 ± 0.23</td>
<td>4.71</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>t-PA:Ac (%)</td>
<td>92.86 ± 8.71</td>
<td>76.58 ± 9.61</td>
<td>6.42</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>t-PA:Ag (%)</td>
<td>4.8 ± 0.48</td>
<td>3.26 ± 0.65</td>
<td>4.25</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>PAI-1:Ac (AU/mL)</td>
<td>4.8 ± 3.14</td>
<td>11.56 ± 3.56</td>
<td>5.63</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>PAI-1:Ag (ng/mL)</td>
<td>8.97±1.34</td>
<td>5.18±0.84</td>
<td>5.93</td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Fig. 1: Mean value of the pre and post test values of BMI, PT, PTT, tPA: Ac and tPA: Ag fibrinogen, vWF-Ag, PAI-1: Ac and PAI-1: Ag in the training group.
Table 2: Mean value and significance of the pre and post test values of BMI, PT, PTT, tPA:Ac and tPA:Ag fibrinogen, vWF-Ag, PAI-1:Ac and PAI-1:Ag in the control group.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>t-value</th>
<th>Significant</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg / m²)</td>
<td>35.75 ± 5.51</td>
<td>35.63 ± 5.71</td>
<td>0.88</td>
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<tr>
<td>PT (s)</td>
<td>10.32 ± 0.60</td>
<td>10.53 ± 0.82</td>
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<tr>
<td>PTT (s)</td>
<td>22.28 ± 2.64</td>
<td>22.45 ± 2.15</td>
<td>0.66</td>
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<tr>
<td>tPA:Ac (IU/mL)</td>
<td>5.42 ± 0.37</td>
<td>5.61 ± 0.62</td>
<td>0.92</td>
</tr>
<tr>
<td>tPA:Ag (ng/mL)</td>
<td>3.85 ± 0.71</td>
<td>3.95 ± 0.84</td>
<td>0.85</td>
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<tr>
<td>Fibrinogen (mg/mL)</td>
<td>4.10 ± 0.72</td>
<td>3.82 ± 0.53</td>
<td>0.78</td>
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<tr>
<td>vWF-Ag (%)</td>
<td>93.16 ± 7.85</td>
<td>92.94 ± 7.04</td>
<td>0.62</td>
</tr>
<tr>
<td>I:Ac (AU/mL)</td>
<td>4.72 ± 0.51</td>
<td>4.61 ± 0.51</td>
<td>0.61</td>
</tr>
<tr>
<td>I:Ag (ng/mL)</td>
<td>19.86 ± 3.44</td>
<td>19.65 ± 2.92</td>
<td>0.56</td>
</tr>
<tr>
<td>HBA1c (%)</td>
<td>8.75±1.68</td>
<td>8.64±1.26</td>
<td>0.83</td>
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</table>

Fig. 2: Mean value of the pre and post test values of BMI, PT, PTT, tPA: Ac and tPA: Ag fibrinogen, vWF-Ag, PAI-1: Ac and PAI-1: Ag in the control group.

Table 3: Mean value and significance of the post test values BMI, PT, PTT, tPA:Ac and tPA:Ag fibrinogen, vWF-Ag, PAI-1:Ac and PAI-1:Ag in the training and control groups.

<table>
<thead>
<tr>
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<th>Mean ± SD</th>
<th>t-value</th>
<th>Significant</th>
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<tbody>
<tr>
<td></td>
<td>Training group</td>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg / m²)</td>
<td>31.14 ±5.51</td>
<td>35.63 ± 5.71</td>
<td>5.34</td>
</tr>
<tr>
<td>PT (s)</td>
<td>12.18 ± 0.96</td>
<td>10.53 ± 0.82</td>
<td>4.11</td>
</tr>
<tr>
<td>PTT (s)</td>
<td>25.76 ± 2.91</td>
<td>22.45 ± 2.15</td>
<td>4.42</td>
</tr>
<tr>
<td>tPA:Ac (IU/mL)</td>
<td>6.5 ± 0.24</td>
<td>5.61 ± 0.62</td>
<td>3.47</td>
</tr>
<tr>
<td>tPA:Ag (ng/mL)</td>
<td>4.57 ± 0.67</td>
<td>3.95 ± 0.84</td>
<td>3.82</td>
</tr>
<tr>
<td>Fibrinogen (mg/mL)</td>
<td>2.26 ± 0.23</td>
<td>3.82 ± 0.53</td>
<td>3.45</td>
</tr>
<tr>
<td>vWF-Ag (%)</td>
<td>76.58 ±9.61</td>
<td>92.94 ± 7.04</td>
<td>5.63</td>
</tr>
<tr>
<td>I:Ac (AU/mL)</td>
<td>3.26 ± 0.65</td>
<td>4.61 ± 0.51</td>
<td>3.58</td>
</tr>
<tr>
<td>I:Ag (ng/mL)</td>
<td>11.56 ± 3.56</td>
<td>19.65 ± 2.92</td>
<td>4.21</td>
</tr>
<tr>
<td>HBA1c (%)</td>
<td>5.18±0.84</td>
<td>8.64±1.26</td>
<td>3.75</td>
</tr>
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</table>

Fig. 3: Mean value of the post test values BMI, PT, PTT, tPA:Ac and tPA:Ag fibrinogen, vWF-Ag,PAI-1:Ac and PAI-1:Ag in the training and control groups.
Discussion:

Obesity independently increases the risk of developing diabetes 10-fold compared with that for patients who are normal weight (Richelle, J., et al., 2009). Moreover, abnormalities in coagulation and fibrinolysis may play an important role in the risk of cardiovascular event in obese subjects (Lee, IM, et al., 2001). We found a significant reduction in fibrinogen after weight reduction. Our findings were in agreement with previous studies.

Weight reduction contributes to a decrease in CVD-related morbidity through improvement of fibrinolytic abnormality and endothelial dysfunction (Barbeau, P., et al., 2002). Dietary therapy, physical activity and combination therapy (diet and physical activity) have been adopted as weight reduction regimens (Clinical guidelines on the identification, 1998). Weight loss in obese patients can therefore be considered a very effective strategy to improve the platelet abnormalities linked to insulin resistance (Anfossi, G., et al., 2009).

In the present study, after weight reduction, tPA activity and tPA antigen were increased and PAI-1 activity and antigen were decreased. Murakami et al. reported that PAI-1 activity and t-PA antigen values positively correlated with BMI and fat tissue mass. These high values were reduced after weight reduction. A significant positive correlation between the percentages of changes in BMI, waist circumference and fat tissue mass and that in PAI-1 activity was observed (Murakami, T., et al., 2007). Our study also showed similar results. Weight reduction enhances fibrinolysis by increasing tPA activity and decreasing PAI-1 activity.

Regarding the results of the current study concerning the PT and PTT were in accordance with the results of Piccone et al., 2005; Stratton, et al., 1991). However, there was a significant reduction of vWF. These results are in agreement with the results of Paton et al. and Saenko et al. reported that it is possible that the active cool down results in an increase in hepatic blood flow and clearance of vWF-Ag (Paton CM, et al., 2004; Saenko, EL., et al., 1999).

The results of the current study regarding fibrinogen revealed that weight reduction led to decrease in fibrinogen concentration, this finding agreed with DeSouza, et al., showed that plasma fibrinogen concentration is lower in physically active than in sedentary postmenopausal women and age-related elevation in fibrinogen levels is twice as great in the sedentary as in the physically active women(DeSouza, CA, et al., 1998). It has been suggested that the favorable association between plasma fibrinogen levels and regular exercise are likely due to lower body fatness (Stefanick, ML, et al., 1995; Krobot, K., et al., 1992).

Finally, the results of the present study regarding HBA1c showed that weight loss resulted in decrease in HBA1c, this result confirmed by Younger et al. reported that increased physical activity leads to improvement in insulin resistance and increase in muscle oxidative capacity which are likely contribute to the beneficial effects of exercise training on insulin action (Youngren, J., et al., 2001). Also, Kriska et al. confirmed that physical activity in obese non-insulin dependent diabetes mellitus decreased blood glucose level through improving insulin sensitivity and decreasing deposition of total fat and intra-abdominal fat. Also, physical activity is negatively associated with insulin concentration as a defense mechanism (Kriska, A., et al., 2001). However, Roland, et al., stated that exercise training improves insulin sensitivity and glycemic control, increases muscle mass, strength and endurance (Roland, J., et al., 2004). Also, Sato, et al., and Short, et al., found that physical exercise promotes utilization and lowering of blood glucose. This improvement in insulin action was attributed to the increase in insulin sensitive glucose transporter on the plasma membrane and oxidative enzymes in skeletal muscle (Sato, Y., et al., 2003; Short, K., et al., 2003). While, Albu, et al., mentioned that lifestyle modifications with diet and exercise are essential part of the management of the diabetic obese patient as weight loss leads to improvement in the glucose tolerance, insulin sensitivity, reductions in lipid levels (Albu, J. and N.,Raja-Khan, 2003).

Conclusion:

Weight reduction improves glycemic control, coagulation and fibrinolytic parameters in obese non-insulin dependent diabetic patients.

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References


