EVEN A SUB-ADAPTIVE MINIMAL EXERCISE IS FAVOURABLE FOR AMELIORATION OF DIABETIC HYPERGLYCAEMIA, DYSLIPIDEMIA AND OXIDATIVE STRESS BUT WITH SOME LOAD ON RENAL FUNCTION

It has been realised since sometime that, regular, non-exhaustive, physical exercise is of great benefit. Unquestionable evidence for the effectiveness of regular physical activities in the prevention of primary and secondary complications of several chronic diseases like cardiovascular disease, diabetes, cancer, hypertension, obesity, depression, osteoporosis and premature death are forthcoming (Warburton et al., 2006). Exercise essentially enhances glucose uptake and utilization by muscle and the first observation that gave evidence to this is of Chauveau and Kaufman (1887), who showed a substantial decrease in the concentration of glucose in the blood draining masseter muscle of horses chewing hay. The role of insulin in glucose uptake by muscle was shown by Burn and Dale (1924) and Cori et al. (1924). More diabetic individuals are turning to intense physical activity with increasing frequency as a consequence of increasing emphasis on fitness and competitive sports.

There are two aspects of diabetic therapy: 1) effective reduction of the state of hyperglycaemia 2) keep the body fats under control as, uncontrolled hyperglycaemia together with fat deposition may lead to chronic long term secondary complications targeting organs like kidney, eyes, nerves, heart and blood vessels (Yki-yar vinen, 1998). Exercise, along with diet medication has been considered as of great importance for diabetic individuals (Joslin et al., 1959). The American Diabetes Association (1997) has been recommending regular but controlled exercise to diabetic patients as, it is supposed to have a
beneficial role in reducing the risk of secondary complications. The intensity of recommended exercise may however vary from individual to individual depending on severity of diabetic complications and overall health of the individual. Exercise has now been increasingly thought of as therapeutic approach in various metabolic disorders like diabetes and obesity due to its low cost and non-pharmacological actions (Normand et al., 2001).

No doubt, remarkable progress has been made in elucidating the mechanisms of regulation of glucose transport in muscle. However, there is still glaring lacunae regarding insulin and exercise mediated mechanisms of glucose transport into muscle. There appears to be many unexplained phenomena relevant to glucose transport and, as opined by Holloszy (2003), "there is no danger that investigators old or young will ever run out of work". This gave the necessary motivation and impetus to assess the effect of swimming exercise on diabetic animals on a holistic basis involving glycaemic regulation, glucose tolerance, insulin response, carbohydrate and lipid metabolisms, oxidative stress and serum markers of hepatic and renal dysfunction.
Results

Glycaemic status (Table 8.3)
Exercise had no significant effect in the fasted state of non-diabetic animals though, hyperglycaemia was the feature in the fed state. Diabetic animals showed significantly high glycaemic status and, exercise though did not alter the glycaemic status to any extent in fed state, brought about normoglycaemia in the fasted state.

Glucose tolerance test (GTT) (Figs. 8.1, 8.2; Table 8.5)
The glucose tolerance curve of DC+S animals was intermediate in position between NC and NC+S on one side and DC on the other. Accordingly, the area under curve which was very great in DC animals was significantly reduced towards NC level in DC+S animals. The favorable influence of swimming exercise in DC animals was clear from the recorded significantly high glucose clearance rate in DC+S animals.

Insulin response test (IRT) (Figs. 8.3, 8.4; Table 8.6)
Like in GTT, in insulin response curve as well, the position of DC+S was intermediate to those of NC groups of animals and of DC animals. The area under curve, which was high in DC was minimized in DC+S. further, the glucose clearance rate under an insulin challenge was also significantly high in DC+S animals.

Immunoblot analysis of cytosolic GLUT-4 (Figs. 8.5A, B)
Immunoblot analysis of cytosolic GLUT-4 expression showed non-significant decrease in NC+S animals and significant decrease in DC animals. Exercised DC animals (DC+S) showed a significant increment.
Carbohydrate metabolism (Figs. 8.6, 8.7; Table 8.7)

Glycogen contents of liver, muscle and kidney were significantly decreased in DC animals. Exercise in NC and DC animals increased the glycogen contents. In correspondence, phosphorylase activity increased significantly in DC animals and decreased in NC+S and DC+S animals from the NC and DC levels respectively. Glucose-6-phosphatase activity was increased in the order, NC < NC+S < DC < DC+S.

Tissue protein contents (Table 8.7)

The protein content was decreased significantly in liver, muscle and kidney of DC animals. Whereas E tended to decrease tissue protein contents in NC animals while, it tended to increase in DC animals.

Hepatic, muscle and kidney lipid contents were significantly decreased in both the exercised groups (NC+S and DC+S) with diabetic induction itself increasing the tissue glycogen contents. In contrast, though tissue cholesterol content was also increased in DC animals, E in DC animals significantly decreased the cholesterol contents while, E in NC animals significantly increased the cholesterol contents.

Serum Lipid profile (Table 8.8)

Serum levels of TG and all cholesterol fractions were significantly increased in diabetic animals. Whereas exercise in NC animals, tended to increase serum levels of TG and all cholesterol fractions, the same in DC animals decreased serum TG and cholesterol fractions.
Serum hormone profile (Table 8.4)

Insulin, Corticosterone (Cort), Oestrogen (E2) and Progesterone (P4)

There were differential changes in all the hormones. Insulin titre was increased significantly in NC+S+M while significantly decreased in DC animals with a further decrease in DC+S+M. Corticosterone was increased in NC+S+M, DC animals in the order DC>NC+S+M. There was significant decrease in DC+S+M animals. Oestrogen was increased significantly in DC animals, which further increased significantly in DC+S+M. Progesterone increased significantly in NC+S+M and was decreased significantly in DC animals. The P4 titre was further reduced significantly in DC+S+M.

Oxidative stress parameters

Lipid peroxidation (LPO) (Fig. 8.7)

Hepatic, muscle and kidney LPO levels were significantly increased in diabetic condition while, E in both NC and DC animals tended to decrease tissue levels of LPO significantly.

Non-enzymatic antioxidant (Table 8.11)

Reduced glutathione (GSH)

Both diabetes and exercise in non-diabetic animals tended to decrease tissue GSH contents significantly in the former. Exercise of DC animals however, significantly decreased GSH contents liver, muscle and kidney.

Enzymatic antioxidants (Table 8.10)

Catalase (cat), superoxide dismutase (SOD) and Glutathione peroxidase (GPx)

As in the case of GSH, even the activity of enzymatic antioxidants was significantly decreased in diabetes and, whereas exercise tended to decrease the
levels of activity of all the three enzymes in NC, it tended to increase the levels of activity in DC animals.

**Serum markers of hepatic function (Table 8.12)**

**SGPT, SGOT, ALP and ACP**

There was significant increase in serum markers of hepatic function in diabetics. Whereas E increased significantly the serum levels of all the enzymes in NC animals, the same significantly decreased the serum levels of all the enzymes in Dc animals.

**Serum markers of renal function (Figs. 8.8, 8.9)**

**Urea and Creatinine**

The serum levels of both urea and creatinine increased significantly in all experimental animals in the order DC+S > DC > NC+S > NC.

**Histology of Pancreas (Plate 8)**

Swimming exercise did not bring about any noticeable change in the histoarchitecture of pancreatic islets. However, diabetic induction was marked by islet disruption marked by islet cell death and appearance of intercellular spaces. Diabetic animals subjected to swimming exercise showed better organized islets with less marked cell death.
Table 8.1: Body weight (g), food intake (g/animal/day) and water intake (ml/animal/day) in all the experimental groups

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>INITIAL BW</th>
<th>FINAL BW</th>
<th>FOOD INTAKE</th>
<th>WATER INTAKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>253.3±5.9</td>
<td>263.3±7.27</td>
<td>16.15±0.01</td>
<td>35.56±1.15</td>
</tr>
<tr>
<td>NC+S</td>
<td>256.12±10.21</td>
<td>258.23±8.11</td>
<td>18.11±0.002</td>
<td>40.58±0.24</td>
</tr>
<tr>
<td>DC</td>
<td>186.67±17.09</td>
<td>189.86±6.012</td>
<td>25.13±0.33</td>
<td>73.5±0.12</td>
</tr>
<tr>
<td>DC+S</td>
<td>210±12.13</td>
<td>225±4.44</td>
<td>21.57±0.058</td>
<td>58.21±1.24</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC

Table 8.2: Relative weights (g/100g of body weight) of liver, muscle, kidney, spleen and adrenal of all the experimental groups

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>LIVER</th>
<th>MUSCLE</th>
<th>KIDNEY</th>
<th>SPLEEN</th>
<th>ADRENAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>2.22±0.14</td>
<td>0.49±0.01</td>
<td>1.68±0.033</td>
<td>0.31±0.07</td>
<td>0.018±0.0014</td>
</tr>
<tr>
<td>NC+S</td>
<td>2.75±0.15</td>
<td>0.58±0.042</td>
<td>1.54±0.057</td>
<td>0.37±0.087</td>
<td>0.19±0.0015</td>
</tr>
<tr>
<td>DC</td>
<td>3.36±0.001c</td>
<td>1.015±0.02b</td>
<td>0.89±0.01c</td>
<td>0.27±0.006</td>
<td>0.031±0.0010c</td>
</tr>
<tr>
<td>DC+S</td>
<td>2.98±0.15</td>
<td>0.97±0.051</td>
<td>1.21±0.024</td>
<td>0.31±0.0034</td>
<td>0.029±0.0012</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC
Table 8.3: Levels of Fasting and Fed Serum Glucose (mg/dl) in Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>FASTING</th>
<th>FED</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>93.97±3.50</td>
<td>113.37±3.19</td>
</tr>
<tr>
<td>NC+S</td>
<td>91.15±2.24</td>
<td>127.79±2.45c</td>
</tr>
<tr>
<td>DC</td>
<td>443.33±31.22c</td>
<td>655.33±7.70c</td>
</tr>
<tr>
<td>DC+S</td>
<td>97.31±1.92®</td>
<td>603±6.12®</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE. 
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming 

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0006 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC

Table 8.4: Serum hormone profile of Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>INSULIN</th>
<th>CORTICOSTERONE</th>
<th>ESTRADIOL</th>
<th>PROGESTERONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>0.349±0.014</td>
<td>8.383±0.59</td>
<td>0.197±0.009</td>
<td>66.68±3.483</td>
</tr>
<tr>
<td>NC+S</td>
<td>0.424±0.030b</td>
<td>10.11±0.385b</td>
<td>0.21±0.007</td>
<td>80.39±3.583c</td>
</tr>
<tr>
<td>DC</td>
<td>0.164±0.0128c</td>
<td>24.67±1.46c</td>
<td>1.99±0.072c</td>
<td>54.23±1.75c</td>
</tr>
<tr>
<td>DIA + S</td>
<td>0.124±0.0030®</td>
<td>18.05±1.36®</td>
<td>2.22±0.078®</td>
<td>40.62±1.538®</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE. 
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming 

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC
Figure 8.1: Serum glucose levels in response to oral glucose tolerance test (OGTT) within a time range of 0 to 120 minutes in Exercised Non Diabetic and Diabetic Rats

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, ◊) p< 0.005 •) p< 0.0005 compared to DC

Figure 8.2: Area under curve for OGTT in Exercised Non Diabetic and Diabetic Rats

NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
Figure 8.3: Serum glucose levels in response to insulin administration (IRT) within a time range of 0 to 120 minutes of in Exercised Non Diabetic and Diabetic Rats

![Graph showing serum glucose levels in response to insulin administration (IRT) for different groups.](image)

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC = Diabetic Control and DC+S = Diabetic Control+Swimming

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01. ○)

Figure 8.4: Area under curve for IRT in all experimental groups

![Bar chart showing area under curve (IRT) (% of control) for different groups.](image)
Table 8.5: Elevation and clearance rates of glucose during OGTT in cadmium and extract treated diabetic and non diabetic rats.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>RATE OF ELEVATION</th>
<th>RATE OF CLEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>1.21</td>
<td>0.50</td>
</tr>
<tr>
<td>NC+S</td>
<td>1.36</td>
<td>0.83</td>
</tr>
<tr>
<td>DC</td>
<td>9.13</td>
<td>1.97</td>
</tr>
<tr>
<td>DC+S</td>
<td>6.69</td>
<td>4.37</td>
</tr>
</tbody>
</table>

Table 8.6 Elevation and clearance rates of glucose during IRT in cadmium and extract treated diabetic and non diabetic rats.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>RATE OF CLEARANCE</th>
<th>RATE OF ELEVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>2.1</td>
<td>0.56</td>
</tr>
<tr>
<td>NC+S</td>
<td>2.27</td>
<td>0.57</td>
</tr>
<tr>
<td>DC</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>DC+S</td>
<td>3.07</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Table 8.7: Tissue Protein and Glycogen content (mg/100 mg tissue) in Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Liver</th>
<th>Muscle</th>
<th>Kidney</th>
<th>Liver</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>16.39±1.24</td>
<td>9.76±1.42</td>
<td>10.40±1.10</td>
<td>2.18±0.10</td>
<td>0.93±0.035</td>
</tr>
<tr>
<td>NC+S</td>
<td>14.87±0.67</td>
<td>5.37±0.47*</td>
<td>6.6±0.81*</td>
<td>2.15±0.175</td>
<td>1.194±0.178b</td>
</tr>
<tr>
<td>DC</td>
<td>13.90±0.87</td>
<td>5.51±0.73*</td>
<td>10.043±1.58</td>
<td>1.80±0.061*</td>
<td>0.58±0.050c</td>
</tr>
<tr>
<td>DC+S</td>
<td>15.92±0.61</td>
<td>6.43±0.35</td>
<td>10.97±0.70</td>
<td>1.42±0.079@</td>
<td>0.76±0.014@</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S = Non Diabetic Control+Swimming, DC = Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC
Figure 8.5: Hepatic and muscle glycogen phosphorylase activity in Exercised Non Diabetic and Diabetic Rats

Data are expressed as Means±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC

Figure 8.6: Hepatic Glucose-6-phosphatase activity in Exercised Non Diabetic and Diabetic Rats

Data are expressed as Means±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC
Table 8.8: Serum lipid profile (mg/dl) of Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Cholesterol</th>
<th>Triglyceride</th>
<th>HDL</th>
<th>LDL</th>
<th>VLDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>80±2.31</td>
<td>68.67±3.45</td>
<td>50.67±1.76</td>
<td>15±1.73</td>
<td>13.11±1.74</td>
</tr>
<tr>
<td>NC+S</td>
<td>96.86±1.68c</td>
<td>74.36±1.59</td>
<td>30.94±2.15c</td>
<td>52.72±1.78c</td>
<td>16.90±1.26</td>
</tr>
<tr>
<td>DC</td>
<td>97.33±4.34c</td>
<td>140.67±2.34c</td>
<td>45.44±2.60</td>
<td>30.66±0.87c</td>
<td>22.22±2.90c</td>
</tr>
<tr>
<td>DC+S</td>
<td>95.48±2.059</td>
<td>74.12±1.26c@</td>
<td>34.82±1.85c</td>
<td>34.52±2.48c</td>
<td>15.38±1.40c</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S = Non Diabetic Control+Swimming, DC = Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC

Table 8.9: Tissue Cholesterol and Lipid content (mg/100mg tissue) in Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>Cholesterol</th>
<th>Lipid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver</td>
<td>Muscle</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>Muscle</td>
</tr>
<tr>
<td>NC</td>
<td>0.28±0.005</td>
<td>0.12±0.0105</td>
</tr>
<tr>
<td>NC+S</td>
<td>0.52±0.055c</td>
<td>0.21±0.016c</td>
</tr>
<tr>
<td>DC</td>
<td>0.60±0.004c</td>
<td>0.29±0.003c</td>
</tr>
<tr>
<td>DC+S</td>
<td>0.11±0.005®</td>
<td>0.13±0.014®</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S = Non Diabetic Control+Swimming, DC = Diabetic Control and DC+S = Diabetic Control+Swimming
a)p<0.05, b) p< 0.026 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC
Figure 8.7: Levels of LPO in Exercised Non Diabetic and Diabetic Rats

Data are expressed as Mean±SE. NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming.

a) p<0.05, b) p< 0.025, c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05, #) p< 0.025, @) p< 0.01, o) p< 0.005, •) p< 0.0005 compared to DC.

nM of MDA/100mg tissue

Experimental Groups

[Bar graph showing levels of LPO in different experimental groups with statistical comparisons indicated.]
Table: 8.10 Tissue enzymatic anti-oxidant status of Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>LIVER</th>
<th>MUSCLE</th>
<th>KIDNEY</th>
<th>LIVER</th>
<th>MUSCLE</th>
<th>KIDNEY</th>
<th>LIVER</th>
<th>MUSCLE</th>
<th>KIDNEY</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>8.17±0.60</td>
<td>10.37±0.60</td>
<td>5.38±0.39</td>
<td>53.96±2.54</td>
<td>73.12±2.60</td>
<td>26.74±3.10</td>
<td>53.96±2.54</td>
<td>73.12±2.59</td>
<td>26.74±3.10</td>
</tr>
<tr>
<td>NC+S</td>
<td>7.23±0.32</td>
<td>9.34±0.37</td>
<td>6.60±0.22c</td>
<td>28.73±4.16c</td>
<td>66.05±2.12a</td>
<td>20.64±1.64</td>
<td>28.73±4.16</td>
<td>66.05±2.12b</td>
<td>20.64±1.64c</td>
</tr>
<tr>
<td>DC</td>
<td>4.64±0.44e</td>
<td>6.56±0.48e</td>
<td>2.72±0.15e</td>
<td>22.97±2.0c</td>
<td>49.83±2e</td>
<td>13.41±0.87e</td>
<td>2.68±0.3b</td>
<td>7.47±0.90c</td>
<td>1.17±0.24d</td>
</tr>
<tr>
<td>DC+S</td>
<td>6.68±0.47@</td>
<td>5.67±0.44</td>
<td>1.107±0.21@</td>
<td>24.25±2.37</td>
<td>61.37±2.73@</td>
<td>20.47±2.31@</td>
<td>24.25±2.37@</td>
<td>61.37±2.73@</td>
<td>20.47±2.31@</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S = Non Diabetic Control+Swimming, DC = Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p<0.025 c) p<0.01, d) p<0.005, e) p<0.0005 compared to NC and *) p<0.05 #) p<0.025 @) p<0.01, o) p< 0.005*) p< 0.0005 compared to DC
Table 8.11: Tissue non-enzymatic anti-oxidant status (mg/100 mg tissue) in Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>GSH</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver</td>
<td>Muscle</td>
<td>Kidney</td>
</tr>
<tr>
<td>NC</td>
<td>31.14±2.58</td>
<td>14.58±1.83</td>
<td>25.03±1.15</td>
</tr>
<tr>
<td>NC+S</td>
<td>29.98±1.56</td>
<td>13.6±1.32</td>
<td>17.98±3.02a</td>
</tr>
<tr>
<td>DC</td>
<td>11.01±1.29a</td>
<td>13.05±1.38</td>
<td>13.04±1.86a</td>
</tr>
<tr>
<td>DC+S</td>
<td>15.68±0.79®</td>
<td>19.49±1.73®</td>
<td>19.15±2.056®</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p<0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 @) p< 0.025 ##) p< 0.01, c) p< 0.005 * ) p< 0.0005 compared to DC

Table 8.12: Serum Markers of Hepatic Dysfunction in Exercised Non Diabetic and Diabetic Rats

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>SGPT</th>
<th>SGOT</th>
<th>ALP</th>
<th>ACP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>40±4.05</td>
<td>71.33±2.97</td>
<td>204±2.65</td>
<td>8.5±0.87</td>
</tr>
<tr>
<td>NC+S</td>
<td>41.04±1.50</td>
<td>186.87±3.05c</td>
<td>66.92±3.25c</td>
<td>15.51±0.67c</td>
</tr>
<tr>
<td>DC</td>
<td>125±5.87a</td>
<td>290.67±5.79a</td>
<td>471.67±2.34a</td>
<td>12.20±0.61d</td>
</tr>
<tr>
<td>DC+S</td>
<td>61.34±2.143®</td>
<td>196.69±2.62®</td>
<td>222±2.65®</td>
<td>12.81±1.35</td>
</tr>
</tbody>
</table>

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p<0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 @) p< 0.025 ##) p< 0.01, c) p< 0.005 * ) p< 0.0005 compared to DC
Figure 8.8: Serum Urea level in Exercised Non Diabetic and Diabetic Rats

![Urea level graph]

**Experimental Groups**

Data are expressed as Mean±SE

NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC

Figure 8.9: Serum Creatinine level in Exercised Non Diabetic and Diabetic Rats

![Creatinine level graph]

**Experimental Groups**

Data are expressed as Mean±SE

NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming

a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC
Fig. 8.10 (A) Immunoblot analysis of Glut-4 protein expression. (B) Semi quantification analysis of Glut-4 protein using scanning densitometry. Signals of Glut-4 in immunoblot were quantified arbitrarily. Bars represent means of ± S.E. of independent experiments and a representative immunoblot is shown here.

GLUT-4

1  2  3  4

Fig. 8.10 (B)

Data are expressed as Mean±SE
NC = Non Diabetic Control, NC+S= Non Diabetic Control+Swimming, DC= Diabetic Control and DC+S = Diabetic Control+Swimming
a) p<0.05, b) p< 0.025 c) p<0.01, d) p< 0.005, e) p< 0.0005 compared to NC and *) p< 0.05 #) p< 0.025 @) p< 0.01, o) p< 0.005 •) p< 0.0005 compared to DC

LANES | GROUPS
--- | ---
1 | DC
2 | DC+S
3 | S
4 | NC

Glut 4 protein expression normalised to B-actin

EXPERIMENTAL GROUPS

Fig. 8.10(B)
PLATE 8

Figure A: Transverse section of pancreas of non diabetic rat showing an islet. Note the intact islet histoarchitecture (450X).

Figure B: Transverse section of pancreas of rat subjected to exercise. Note the well formed islets with well formed islet cells. (450X)

Figure C: Transverse section of pancreas of diabetic rat. Note the islet cell destruction and the wide intercellular spaces. (450X)

Figure D: Transverse section of pancreas of diabetic rat subjected to exercise. Note the improved morphology showing normal looking islet cells with bettered islet integrity (450X).
Discussion:

Physical activity could be of great benefit for overall health and disease prevention or protection against. However, physical activities are also likely to contribute to oxidative damage and prove contra to maintenance of health. So physical activity or exercise has been the topic of many research investigations and, in one of recent reviews, Urso et al. (2003) have summed up with a statement "exercise may or may not result in harmful oxidative stress, and antioxidants may or may not reduce oxidative stress if it recurred at all. We are uncertain whether an increase in oxidative stress that occurs with exercise is necessary for muscle adaptation to occur, or whether it is harmful, causing muscle damage that impairs the ability to perform or train. There is growing evidence that free radicals can serve as signals that stimulate adaptive processes (Jeehem, 2000). We do not know at what level of increased oxidative stress the potential benefits will outweigh the risks". Apparently, events associated with exercise is a double edged sword as, above an optimum physiological acceptance it could lead to a pro-oxidant state while, moderate indulgence within the level of physiological acceptance may prove to be antioxidant. The matter of the fact seems to be, moderation and regulated exercise, especially in diabetic complications which involve oxidative stress both as cause and effect. A moderate regimen of exercise may prove beneficial, which can also help exercise regulation over glycaemic status, the primary cause of many secondary diabetic complications. In this, alloxan / Streptozotocin induced type I diabetic rats, serve as ideal models to study the effects of moderated exercise. Moreover, rats are considered natural swimmers and hence, many experimental protocols involving
swimming exercise have been in vogue. (Nikolovshi et al., 1996; Brain et al., 1997).
So in the present study, a swimming exercise regimen of 30 mts duration per day for
a period of 15 days, has been employed to assess the impact on both non-diabetic
and diabetic rats.

The present experimental paradigm of 15 days of swimming exercise has
shown no change in glycaemic status in overnight starved non diabetic rats while,
the glycaemic status of the fed state showed milder hyperglycaemia. However, the
same schedule in diabetic rats showed normoglycaemia in the starved state and
milder reduction in glucose level in the fed state. The average of fed and fasted state
reveals no change in the glycaemic status of the exercised non diabetic rats
compared to non exercised ones. However, in diabetic rats, the average glucose
level is significantly lowered in exercised rats compared to non exercised ones.
Apparently, mild exercise has a favourable influence in diabetic animals in lowering
the glucose level. Similar effect of exercise on glycaemic levels of diabetic animals
and humans has also been observed in other studies (Fischer et al., 2003; Broderich
and Nadean, 2006). Even though the non-diabetic animals have not shown much
glycaemic change in the short duration experimental paradigm, these animals do
nevertheless manifest a better glucose clearance as seen from the almost doubled
 glucose clearance rate (0.489/minute in non exercised to 0.839 in exercised) under
a glucose tolerance test. This is confirmed by the relatively greater glucose
clearance and elevation rates seen during an insulin response test, compared to
non-exercised animals. This increased insulin sensitivity is further supported by the
increased insulin level, promoting increased glucose withdrawal. This increase in
insulin is contrary to the decrease registered after a single bout of acute exercise (Broderich and Nadean, 2006). The increased insulin action and removal of blood glucose are well reflected in the increase in tissue glycogen content and decrease in glycogen phosphorylase activity. Apparently, at the level of exercise employed in the present study, there is a sparing effect on tissue glycogen and, lipid and blood glucose seem to be the choice metabolites utilized.

Increased glucose uptake and glycogenesis seen herein are adequately supported by the significant decrement in cytosolic GLUT-4 suggesting increased membrane insertion and glucose influx. Such an exigency of exercise induced increase in GLUT-4 expression and glucose uptake are well recorded (Han and Pronen, 1998; Richter et al, 2001). The presently observed increase in total serum cholesterol, LDL, VLDL and triglycerides coupled with decrease in tissue total lipid and cholesterol contents, are indicative of increasing lipid mobilization in the wake of exercise induced increased energy demand.

Though decrease in tissue lipid is an indication of increased lipolysis, the increase in serum lipid levels attests to under utilization. Apparently, the balance is tilted more towards lipolysis rather than lipid utilization. It is presumable that, continuous regular exercise marked by gradual shift towards lipid utilization and with persistent chronic exercise (duration dependent on the type and degree of exercise activity), gradual adaptation sets in wherein, efficient lipid utilization ultimately keeps pace with lipid mobilization. With exercise induced metabolic adaptation, serum lipids are expected to be lower as has been shown by other workers involved with studies on exercise adaptation (Horowitz and Klein, 2000; Aginilo et al., 2003;
Hernandez-Torres et al., 2009). It is likely that, sub maximal exercise insufficient to bring about adaptive change could result in higher levels of plasma glucagon and catecholamines, which could contribute to increased lipolysis and higher serum lipid levels. In fact, Winder et al. (1979), have recorded increased plasma glucagon and catecholamine in individuals subjected to sub maximal exercise.

Sub adaptive exercise regimen may also contribute to some oxidative stress initially though, adaptive and trained exercise might relieve oxidative stress and create an antioxidant state. The present study on swimming exercise, though do not seem to have caused any increase in lipid peroxidation, marker of oxidative stress, has nevertheless, revealed some oxidative stress marked by significant decrement in catalase activity in liver, muscle and kidney and GSH depletion in Kidney along with an increase in serum corticosteroid titre. This may have some relevance in the observed elevation in serum lipid profile. However, favourable influence of swimming exercise is also observable in the form of increase in GPx activity in all the three organs along with an increase in SOD activity in kidney and elevation in Serum $E_2$ level. In fact, studies on exercise induced alterations in endogenous antioxidant status and oxidative stress are inconclusive, with few studies suggesting generation of some oxidative stress, and others suggesting upregulation of antioxidant status (Sen, 1995; Urso and Clarkson, 2003; Gromez-cabrera et al., 2008). Apparently, initial phases of sub maximal training exercise prior to adaptation may result in some oxidative stress while, long term exercise may lead to adaptation and favourable whole body antioxidant status.
Clearly, the duration and intensity of exercise employed in the present study are sub-adaptive as also denoted by the increase in serum markers of renal (urea and creatinine) and hepatic (SGOT and ACP) functional disturbances. It is likely that, a longer duration of the swimming exercise could lead to favourable changes caused due to exercise adaptation and attendant benefits. These changes may simply indicate an initial mild effect on hepatic and renal function as part of exercise adaptations as, there are no reports in literature of exercise induced hepatic and renal dysfunctions.

Through the present exercise regimen appears to be sub-maximally adaptive in non-diabetic animals, the same regimen appears to be significantly beneficial to diabetic animals as can be realised from the recorded observations. Diabetic animals in the present study have significantly very high hyperglycaemia in both overnight fasted or fed states. Apparently, even an overnight fasting does not succeed in bringing down the glycaemic level substantially. However, exercised animals subjected to an overnight fast has significant favorable influence, as marked by the normoglycaemia in such animals. The effect of exercise on fed diabetic animals is however very minimal suggesting, diet regulation in combination with exercise to be of great merit in the management of diabetic hyperglycaemia. In fact, favorable influence of exercise on glucoregulation and hormonal changes, has been forthcoming from some recent studies (Guelfi et al., 2005; Gulve, 2008; Harmer et al., 2007). The significant hypoglycaemic effect of swimming in overnight starved diabetic rats is well co relatable with the recorded significant decrement in glucose elevation rate and increment in glucose clearance rate in these animals, compared
to non-exercised diabetic animals during an oral glucose tolerance test. This attests to potentiated insulin sensitivity and glucose disposal from circulation. Further, the observed glucose elevation subsequent to an insulin challenge induced glucose clearance in exercised diabetic rats, as against no elevation during the time period of evaluation in unexercised diabetic animals during an insulin response, also bespeaks of improved glucagon response to insulin, compromised in diabetic animals (Quesada et al., 2008).

Improvement in tissue glycogen load concomitant to hypoglycaemia suggests augmented glucose uptake and conversion to glycogen. Decreased glycogen phosphorylase activity further attests to the favorable influence of exercise on carbohydrate metabolism. Apparently, an exercise regimen improves glucose disposal mechanisms in diabetic rats despite no improvement in insulin titer. It is likely that, either potentiated insulin sensitivity and/or alternate insulin independent mechanism of glucose uptake could be inferred. This is well substantiated by the herein observed significant increase in GLUT-4 level in exercised diabetic animals compared to non-exercised diabetic animals. Inferably, increased GLUT-4 translocation to sarcolemma as well as increased GLUT-4 synthesis can be presumed as the favorable effects of exercise in diabetic animals. This concept stands vindicated by the many recent studies demonstrating exercise induced increased GLUT-4 translocation as well as GLUT-4 mRNA expression in diabetic animals as well as non-diabetic subjects or animals (Chebalin et al., 2000; Kraniou et al., 2000, 2006; Macean et al., 2000, 2002; Tomas et al., 2002; Barth et al., 2004). The increased glucose uptake seen in the present study despite the poor insulin
status, suggests the participation of alternate signaling molecules that could activate GLUT-4 vesicle translocation. In this context, many recent studies have provided evidence for AMPK and CAMK mediated exercise induced insulin independent signaling pathway in GLUT-4 translocation to membrane (Hayashi et al., 1997; Musil et al., 2001; Richter et al., 2001; Tomas et al., 2002; Holloszy, 2003; Josen and Richter, 2005).

The favorable influence of exercise, seen with reference to diabetic glycaemic status, glucose uptake and carbohydrate metabolism, is also well reflected in the improved lipid profile. Both tissue cholesterol and lipids as well as serum cholesterol, LDL, VLDL and triglyceride have all shown significant reduction in exercised diabetic rats suggesting a lipid lowering effect of exercise in diabetic animals. Unlike in non-diabetic animals, swimming exercise of 30 minutes duration for 15 days appears to be adaptive in diabetic animals marked by carbohydrate conservation and lipid utilization. It is likely that, blood glucose may also serve as an adequate metabolic substrate along with lipid. Unlike in non-diabetic animals, where the 15 day schedule exercise was found to be non adaptive marked by increased lipid mobilization rather than utilization, the same schedule in diabetic animals is adaptive and tilts the scale towards greater lipid utilization than mobilization. Supportive evidence comes from the many studies demonstrating lowered lipid profile in exercised diabetic subjects (Laakosonen et al., 2000; Laakosonen, 2003; Gordon et al., 2008).

Diabetic complications are marked by increased oxidative stress as denoted by increased LPO and decreased content and activity of non-enzymatic and enzymatic antioxidants respectively. The present observation of significant
decrement in LPO and increase in endogenous antioxidants, with GPx activity depicting even an above normal level, are in agreement with the many reports on exercise induced amelioration of oxidative stress (Gul et al., 2002; Maritim et al., 2003; Coskun et al., 2004; Black et al., 2005; Chang et al., 2007; Gordon et al., 2008).

Interestingly, swimming exercise could significantly reverse the diabetes induced increase in serum markers of hepatic functions but, serum markers of renal dysfunctions show a further increase from the diabetic level. Apparently, physical exercise in diabetic animals seems to have some functional stress on the renal tissue. The observed amelioration of oxidative stress and improvement of hepatic functions stand in good stead by the recorded decrease in serum corticosterone level and increase in oestrogen titre.

Overall, the present observations suggest a favorable influence of exercise in glucoregulation, lipid profile and oxidative stress in animals with Type 1 diabetes. Based on these, exercise may be considered as of greater therapeutic value in ameliorating diabetic manifestation.