The Egyptian Journal of Hospital Medicine (2007) Vol., 27: 245– 254

Lipids and oxidative stress in blood serum of alloxan-induced diabetic rats: possible effects on liver and kidney tissues.

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Abstract

Experimental diabetes mellitus in rats was produced by a single dose of 200 mg of alloxan /kg body weight given intraperitoneally as an aqueous solution. The diabetic rats showed abnormal high blood glucose and variable increments in serum total lipids as well as in other serum lipid constituents particularly the triglycerides.

Certain pathological abnormalities could be detected in both liver and kidney, particularly when the disturbances in glucose and lipid metabolism were more pronounced in a group of diabetic rats that received no insulin treatment {NIT} or after four weeks of the onset of diabetes. On the other hand, putting the group of diabetic rats on an insulin regimen from the start of the diabetic condition resulted in a significant restoration of most evaluated parameters to values almost similar to those of normal control animals. Diabetic rats receiving no insulin treatment showed a markedly significant loss in body weight; and started to gain body weight gradually when put on the proper insulin regimen.

Introduction

Diabetes mellitus is a disease of different etiology, it may arise as a result of abnormalities in a number of intrinsic factors as stress; pregnancy or disorder in β cells function in synthesis and secretion of insulin. Experimentally, the disease can be induced through the destruction of β cells in the islets of Langerhans by diabetogenic agents such as alloxan. Much attention is given to studies on biochemical abnormalities that associate the disease as well as the proper control of its course, since if the diabetic condition is not well controlled a number of undesirable dangerous complications such as atherosc-lerosis, heart disease, retinopathy and hepatic histopathological changes could be frequently encountered among diabetic patents. The present study deals with investigations on biochemical abnormalities in blood glucose, serum total lipids and their main constituents namely: cholesterol, triglycerides, phosp-holipids together with follow up of pathological changes in both the liver and kidney.

Also, the value of introduction of insulin treatment at the onset of the diabetic condition, or at the later period after alleviating the diabetic state and on its complications was investigated.

Material and methods

Albino rats of both sexes three to five months of age and weighing 300 to 320 gm were used. Animals were left to feed ad libitum. Rats were rendered diabetic through the administration of a single dose of alloxan (200 mg / Kg body weight) injected intrap-eritoneally. Blood glucose was estimated by the glucose oxidase method (Trinder, 1969), serum triglycerides, chole-sterol and phosph-olipids were determined by enzymatic colorimetric methods (Takayama 1977); (Wahlefeld 1974); (Flegg 1973) ;(Richmond 1973) while serum total lipids were estimated using sulfophosph-ovanilin method reported by Zoellner and Kirsch (1962).

Insulin when introduced was injec-ted subcutaneously using special insulin needles, and the doses adopted were 1.5

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to 3 IU / rat according to the extent of elevation in its blood glucose level.

Blood samples were collected at weekly intervals from the tail vein as described by Hofmann (1963) and serum was separated after blood clotting and analyzed at once. Fresh liver and kidney specimens were extracted from killed rats, fixed with Bouin Holland as described by Martoja and Martoja (1967) and stained with Haematoxilin and Eosin.

Results

Data for control non diabetic rats (ND rats) are given in Table (1). The data obtained for the different parameters (body weight, blood glucose, serum triglycerides, cholest-erol, phospholipids and total lipids) investigated in the different diabetic groups are given in Table (2).

In diabetic rats receiving no insulin treatment, there was an increase in all biochemical parameters with severe loss in body weight at the end of the 4^{th} week after the onset of the diabetic state (Table, 3). These abnormalities were accompanied with serious pathological alterations in their hepatocytes, marked by microsteatosis (Araya, *et al.* 2004), ectasis of lobular venous centers and cytoplasmic clarification. Also there were swelling of the epithelial cells of the proximal convoluted renal tubules (Moorhead, *et al*., 1986; Craven, *et al.*, 1987) together with glomerular lesions (Mauer, *et al.*, 1981; Mauer, *et al.*, 1984; Ashim, *et al.*, 1990). Besides the death rate among the diabetic rats left without insulin treatment was significantly high (18.2 % by the end of the 12^{th} week from the onset of the disease, Table, 4).

Insulin administration particularly when given early at the onset of the diabetic state caused a significant drop in blood glucose and serum triglycerides to values approaching the normal levels. Also the levels of serum cholesterol and phospho-lipids showed pronounced decrements although remained slightly elevated above normal (Table, 5). Furthermore, all insulin treated diabetic rats gained body weight and showed net decreases in serum glucose and triglyc-erides while the other parameters fluctuated around the normal values (Table, 6). A marked decrease in death rate particu-larly among the diabetic group that received insulin treatment immediately after the onset of the diabetic condition was observed.

The activities and levels of enzy-matic and non-enzymatic antioxidants of all animal groups are presented in Table 1. After induction of diabetes and before initiation of treatment all diabetic rats had a significant decrease in the activities and levels of all the studied parameters, with the exception of SOD being significantly elevated, as comp-ared with normal rats. Treatment with insulin for eight weeks resulted in a significant restoration in most of the evaluated parameters to values that were not different from those of normal control animals.

Hepatopathological changes were alleviated in diabetic rats receiving insulin treatment four weeks after the onset of diabetes and were completely prevented among the diabetic rats put on insulin regimen immediately after the disease.

However the pathological changes in the epithelial cells of proximal renal convoluted tubules were not alleviated under late, (after 4 weeks of the onset of diabetes), insulin treatment. Yet the renal abnormalities were not detected among the diabetic rats treated with insulin immediately after the onset of the diabetes (Lijun Sun *et al.*, 2002).

Table (1) : Levels of biochemical parameters in ND rats

		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	141 -321	61 -129	34 - 106	33 - 116	81 - 192	205 - 429
Mean	207	98	69	66	138	320
± SE	7.2	3.1	2.5	2.5	1.8	4.1

Mean ±SD values of enzymatic and non-enzymatic antioxidants of control rats, and diabetic control and insulin-treated rats before and after 8 weeks of treatment with insulin.

Parametera	Control	Diabetic control		Insulin treated	
		Week 0	Week 8	Week 0	Week 8
GPx (U/g Hb)	12.5±2.50	8.34±1.63[b]	7.55±2.08[a]	7.55±1.92[a]	10.5±1.74[c,d]
GRx (U/g Hb)	4.40±0.27	2.58±0.29[a]	2.66±0.34[a]	2.71±0.25[a]	3.56±0.32[b,c]
SOD (U/g Hb)	0.22±0.05	0.46±0.04[a]	0.44±0.07[a]	0.44±0.08[a]	0.25±0.04[b,c]
CAT (U/g Hb)	1.12±0.30	0.69±0.16[a]	0.66±0.15[a]	0.66±0.12[a]	0.85±0.23[b,c]
GSH (Amol/g Hb)	4.55±0.50	2.31±0.34[a]	2.09±0.37[a]	2.25±0.30[a]	3.95±0.45[b,c]

a GPx:= glutathione peroxidase,
GRx:= glutathione reductase,
SOD =: uperoxide dismutase,
CAT:= catalase,
GSH:= glutathione.

b $p < 0.05$ as compared with control.
c $p < 0.05$ as compared with Week 16 (between groups).
d $p < 0.01$ as compared with Week 0 (within group).

Table (2) :

Levels of biochemical parameters in D rats 1st (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	130 - 300	246 - 466	56 -376	24 - 102	61 - 257	308 - 704
Mean	197	348	119	66	137	460
±SE	6.4	10.1	12.2	3.2	6.7	19.1
Levels of biochemical parameters in D rats 2nd (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	148 - 279	460 -.246	66 - 210	41 - 119	80 - 255	275 -599
Mean	191	320	125	73	140	415
±SE	5.4	9.1	7.4	3.8	7.6	21.7
Levels of biochemical parameters in D rats 3rd (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	143 - 259	210 - 423	72 -252	49 - 202	93 - 207	297 - 626
Mean	184	325	137	76.2	134	411
±SE	5.4	11.5	7.6	5.3	5.1	14.7
Levels of biochemical parameters in D rats 4th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	139 - 245	211 - 424	87 - 195	46 - 88	93 - 185.	333 - 528
Mean	178	310	135	68	136	402
±SE	5.2	12.4	4.5	2.1	4.3	9

Levels of biochemical parameters in D rats 5th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	135 - 241	211 - 420	79 - 168	57 - 106	113 - 183	217 - 517
Mean	177	324	124	78	145	393
±SE	6.4	15.8	6.4	3.5	4.8	15.3
Levels of biochemical parameters in D rats 6th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	132 - 187	422 - 301	79 - 192	40 - 109	111 - 174	338 - 505
Mean	165	351	135	69	143	417
±SE	6.1	13.5	9.7	4.5	4.7	14.4
Levels of biochemical parameters in D rats 7th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	127 - 183	250 - 459	97 - 179	45 - 108	119 - 179	387 - 498
Mean	159	358	140	68.2	143	458
±SE	5.2	17.7	7.7	4.3	4.5	10.1
Levels of biochemical parameters in D rats 8th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	131 - 178	213 - 430	103 - 183	48 - 90	124 - 167	349 - 522
Mean	156	336	151	71	143	456
±SE	4.8	22	7.2	3	4.3	13.8
Levels of biochemical parameters in D rats 9th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	130 - 172	221 - 437	109 - 186	56 - 93	102 - 181	430 - 544
Mean	155	350	154	72.7	145	457
±SE	4.6	20.2	6.6	3.1	6.3	12.6
Levels of biochemical parameters in D rats 10th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	121 - 168	212 - 434	113 - 192	57 - 102	106 - 198	442 - 582
Mean	150	352	154	76	151	475
±SE	4.8	22.2	8.0	4.1	8.5	11.9
Levels of biochemical parameters in D rats 11th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	116 - 164	263 - 429	111 - 197	55 - 114	116 - 195	402 - 520
Mean	143	359	151	83.3	154	453
±SE	5.2	15.6	7.8	5.4	6.8	9.6
Levels of biochemical parameters in D rats 12th (week)						
		Biochemical parameters mg / dl				
	Weight(gm)	Glycemia	Triglycerides	Cholesterol	Phospholipids	Total Lipids
Range	115 -161	279 - 437	114 - 186	54 - 108	130 - 195	425 - 500
Mean	138	345	156	82	157	455
±SE	5.5	17.6	8.6	5.3	6.5	7.6

Table (3) : Statistical studies of biochemical parameters in D rats

Weeks	**1**	**2**	**3**	**4**
Nbr of rats	**33**	**30**	**28**	**27**
Bio-parameters				
Weight range Mean ± SE Variation %	130 - 300 197 6.. 4 - 40.0	148 - 279 191 5.4 -77.0	143 – 259 184 5 .4 -11.1	139 - 245 5.2 -14.0
Glycemia Mean ± SE Variation %	246 - 466 348 10.1 +266	460 -.246 320 9.1 +227	210 – 423 325 11.6 + 232	211 - 424 310 12.5 +216
Triglycerides Mean ± SE Variation %	56 -376 119 12.2 +72	66 - 210 125 7 . 4 126 + 8 1	72 - 252 137 7.6 +99	87 - 195 135 4.5 +96
Cholesterol Mean ± SE Variation %	24 - 102 66 3 . 2 67 + 0 . 0	41 – 119 73 3 . 8 74 + 1 0 . 6	49 - 202 76.2 5. 3 76.3 + 15 .2	46 - 88 68 2 . 1 +3.0
Phospholipids Mean ± SE Variation %	61 - 257 137 6.7 -0.7	80 - 255 140 7.6 141 +1.4	93 - 207 134 5 . 1 -2.9	93 - 185 136 4.3 -1.4
Tot. Lipids Mean ± SE Variation %	308 - 704 460 19.1 +43.8	275 -599 415 2 1 . 7 416 + 2 9 . 7	297 - 626 411 1 4 . 7 412 + 2 8 . 4	333 - 528 402 9.0 +25.6

D= diabetic rats

Table (4) : % of death among D rats non treated with Insulin

Weeks	1	2	3	4	5	6	7	8	9	10	11	12
Remaining rats (week)	33	30	28	27*	20	15	12	12	12	12	11	9
Nbr of death (weekly)	0	3	2	1	0	5	3	0	0	0	1	2
Rate of death / Past week %	0	9	6.7	3.6	0	25	20	0	0	0	8.3	18.2

* 7 rats were withdrawn to be treated with insulin

D= diabetic rats

Weeks	0	1	2	3	4	5	6	7	8
Nbr of rats	9	9	9	7	7	6	6	6	6
Bio-parameters									
Weight range		135 - 193	144 - 199	155 - 200	161 - 216	168 - 227	171 - 232	174 - 235	179 - 239
Mean ± SE	143 - 204	166 6.7	174 6.3	179 6.4	187 7.2	192 8.9	198 9.4	203 9.7	208 9.7
Variation %	176 7.1	-5.7	-1.8	1.7	7.4	9.1	12.5	15.3	10.2
Glycemia		52 - 105	50 - 110	53 - 92	60 - 87	60 - 66	59 - 69	60 - 79	55 - 75
Mean ± SE	265 - 466	78 5.9	80 6.8	70 5.3	68 3.8	63 0.8	64 1.4	66 2.8	66 3.1
Variation %	355 23	-75.0	-77.9	-80.5	-80.8	-82.3	-82.0	-81.4	-81.4
Triglyceride		46 - 101	41 - 111	40 - 65	45 - 67	49 - 71	53 - 80	58 - 83	62 - 80
Mean ± SE	65 - 130	57 6.0	58 7.0	53 2.9	58 2.8	60 3.6	63 3.6	68 3.3	68 2.8
Variation %	81 6.6	-29.6	-28.4	-34.6	-28.4	-26.0	-22.3	-16.0	-16.0
Cholesterol		68 - 108	64 - 103	60 - 88	64 - 82	62 - 80	68 - 90	70 - 90	72 - 94
Mean ± SE	70 - 102	90 4.8	87 4.5	71 3.2	73 2.2	72 2.6	77 2.9	79 2.6	79 3.1
Variation %	90 3.8	0.0	-3.3	-21.1	-18.9	-20.0	-14.5	-12.2	-12.2
Phospholipids		130 - 181	145 - 196	113 - 168	117 - 198	116 - 158	118 - 140	129 - 140	121 - 140
Mean ± SE	125 - 170	160 5.8	171 6.1	150 7.6	152 9.3	133 6.2	129 3.4	132 2.1	131 2.6
Variation %	153 5.3	4.5	11.8	-2.0	-0.7	-13.1	-15.7	13.2	-14.4
Tot. Lipids		306 - 429	308 - 432	327 - 437	339 - 430	340 - 471	350 - 452	360 - 470	365 - 412
Mean ± SE	390 - 485	372 14.7	366 15.6	375 17.1	382 17.7	373 20.0	381 15.0	390 17.0	380 7.5
Variation %	438 11.8	-15.1	-16.4	-14.4	-12.8	-14.8	-13.1	-11.0	-13.2

Table (5) : Insulin treated group after 4 weeks of the onset of the disease

Table (6) :Insulin treated group immediately after the onset of the disease

Weeks	0	1	2	3	4	5	6	7	8
Nbr of rats	7	7	5	5	4	4	3	3	3
Bio-parameters									
Weight range Mean ± SE Variation %	153 - 191 176 5.4	162 - 199 185 5.1 5.1	167 - 198 185 5.9 5.1	172 - 203 190 6.1 7.9	176 - 208 193 8.0 9.6	182 - 213 198 7.8 12.5	186 - 217 205 13.9 16.4	191 - 220 219 ns 24.4	197 - 225 214 ns 21.6
Glycemia Mean ± SE Variation %	235 - 353 289 4.5	61 - 137 81 10.5 71.9	52 - 104 78 10.9 74.0	64 - 124 91 12.7 68.5	63 - 83 72 4.3 75.0	65 - 81 74 3.9 74.3	52 - 104 84 ns 70.9	60 - 102 80 ns 72.3	65 - 80 71 ns 75.4
Triglyceride Mean ± SE Variation %	107 - 175 141 12	48 - 86 67 5.0 52.4	53 - 74 66 3.5 53.2	44 - 68 58 4.4 58.8	54 - 74 61 4.4 56.7	40 - 63 59 2.0 58.1	62 - 69 64 3.39 54.6	46 - 62 56 ns 60.2	45 - 65 57 ns 59.6
Cholesterol Mean ± SE Variation %	46 - 80 66 4.7	67 - 89 80 3.1 21.9	59 - 81 69 3.8 4.5	50 - 77 63 4.4 -4.5	51 - 88 67 7.9 1.5	50 - 74 63 5.4 -4.5	49 - 73 57 10.8 -13.6	66 - 80 72 ns 9.0	66 - 105 81 ns 22.7
Phospholipids Mean ± SE Variation %	93 - 156 156 7.6	124 - 173 154 6.8 22.2	109 - 166 130 10.0 3.1	63 - 184 125 21.0 -0.8	118 - 150 132 7.4 4.7	98 - 130 118 7.5 -6.3	100 - 113 105 5.7 -16.6	112 - 128 121 ns -3.9	130 - 150 138 ns 9.5
Tot. Lipids Mean ± SE Variation %	333 - 428 382 12.4	337 - 408 374 8.7 2.1	317 - 441 344 28.3 9.9	238 - 464 352 36.2 7.8	232 - 429 331 43.2 13.3	295 - 380 344 20.6 9.9	266 - 421 364 7.0 4.7	285 - 385 337 ns 11.7	297 - 403 356 ns 6.8

Discussion

Intraperitoneal administration of single dose of alloxan (200 mg / Kg BW) led to the development of a severe diabetic state (Marliss *et al*., 1981) 48 to 72 hours after alloxan administration accompanied by a significant loss in body weight. The latter could be attributed to disturbances in metabolism associated in insulin deficiency (Davidson and Kaplan, 1977).

Also, it was accompanied with a high percent of death, which had been attributed principally to hypoglycemic phase after alloxan administration as noted and suggested by (Okamoto, 1970)

High death continued during the 1st 2nd and 3rd weeks after the onset of diabetes (Garcia, *et al* 1974). but such rat was significantly lower when insulin treatment was initiated at the onset of the disease (Table 4).

The diabetic hyperglycemia due to insulin deficiency was accompanied with hyper triglyceridemia, an observation also reported by Bragdon and Gordon (1958), and Grundy *et al*. (l979). The increase in serum triglycerides seems to be due to a number of intrinsic factors such as a decrease of triglyceride uptake by adipose tissue, the intensified triglycerides production and release by the liver (Nestel and Steinberg, 1963; Van Tol, 1977; Weiland, *et al.*, 1980).

Elevation in serum cholesterol in the alloxan diabetic rats appeared not be slightly related to the extent of hyperglycemia, most probably to metabolic disturbances corre-lated with abnormalities in the function of enzymatic systems concerned with synthesis and breakdown of cholesterol mainly HMG reductase and HMG synthase (Anderson, *et al.*, 1994; Thomson, 1980).

Besides the accelerated absorption of cholesterol by the intestine has been suggested (Zhang, and Beynen, 1993) to play an important role in the causation of this hypercholesterolemia among diabetic rats. The minor changes in serum phosp-holipids seems to be related to the disturbances in the different phosph-olipase enzymatic activities (Kunz, *et al*., 1994); under the effect of insulin deficiency as well as the concomitant abnormalities in glucose metabolism.

Enforcement of insulin treatment, four weeks after the development of diabetic state, decreased to a limited exte-nt, the rate of death, while when insulin

treatment was adopted immediately after the onset of the disease the rate of death was significantly decreased concomitant with disappearance of pronounced biochemical abnormalities in serum and pathological abnormalities in liver and kidney (Wexler, 1970; Stout, 1979; Wright *et al.*, 1980; Wright *et al*., 1983; Hostetter, 1985; Holthofer, *et al*., 1987).

In this study it is suggested that the biochemical changes in glucose and lipid metabolism that accompany diabetes resulting from insulin deficiency could participate in the development of different undesirable complications affecting various organs, among which are the liver and kidney and endangering the life of patients. Besides, it reveals that insulin treatment and well control of the diabetic conditions, as early as possible from the onset of the disease, could significantly lower the risk of the development of such complications.

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الإجهاد التأكسدي في مصل دم الفئران المصابة بمرض السكر التجريبي بالألوكسان: إمكانية التأثير على نسيجي الكبد و الكليتين .

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بعد ظهور ارتفاع ملحوظ في مستوى جلوكوز الدم عند الفئران المحقونة بالألوكسان Alloxan (200 مع / كغ وزن الجسم)، في تجويف البطن، تبعتها زيادات في مستوى كل من الجليسريدات الثلاثية، الدهون الكلية، الفوسفولبيدات و الكولسترول. صاحب هذه الاضطرابات تغيرات باثولوجية على مستوى نسيجي الكبد و الكليتين، خاصة عند اشتداد الاضطرابات في المجموعة المصابة بمرض السكري غير المعالجة بالأنسولين، أو بعد مضي أربعة أسابيع من حدوث المرض.

من ناحية أخرى المجموعة المصابة بالمرض الخاضعة للعلاج بالأنسولين فور حدوث المرض أبدت تحسنا في عودة مستوى المؤشرات البيولوجية إلى المستوى الطبيعي، باقي الفئران غير الخاضعة للعلاج بالأنسولين فور حدوث المرض، أظهرت انخفاضا في وزنها بصورة معنوية، إلا أنها بدأت تسترد وزنها عند تلقيها العلاج بالأنسولين بعد أربعة أسابيع. باقي المؤشرات البيولوجية، عرفت تراجعا معنويا مقارنة مع المرحلة ما قبل العلاج.