

6. SUMMARY AND CONCLUSIONS

Type 2 diabetes mellitus is a metabolic disorder of fuel homeostasis characterized by hyperglycemia and altered lipid metabolism caused by insulin secretion and actions. Over the last 50 years diabetes is growing rapidly. The estimated worldwide prevalence of diabetes among adults was 285 million (6.4%) in 2010, and this value is predicted to rise to around 439 million (7.7%) by 2030 and Egypt will be ranked as the 10th country worldwide which has the highest number of people with diabetes, making it one of the most serious diseases of humankind. The frequent association of diabetes with obesity has led many investigators to propose that obesity and associated insulin resistance may be responsible for up to 90% of type 2 diabetes. Since skeletal muscle is a key metabolic tissue, accounting for about 80% of total glucose disposal under insulin-stimulated conditions, also adipose tissues and liver play important role in glucose homeostasis, defects of insulin action in these tissues are central to the pathogenesis of type 2 diabetes. Identifying the etiology and the early detection of type 2 diabetes are keys to prevention. Among the trace elements essential for human health, selenium (Se) stands out for its unique biochemistry, its antioxidant capacity and its narrow therapeutic window.

An anti-diabetic impact of dietary selenium supplementation would be expected given both the long track of selenium as insulin – mimetic micronutrient and its antioxidant capacity as constituent of ROS- detoxifying selenoenzymes, suggesting a protective role against oxidative stress – related chronic complications in the progression of diabetes. Contrarily to those expectations, recent epidemiological and intervention studies revealed a surprising association between high plasma selenium levels and type 2 diabetes. The mechanism of the potential diabetogenic effect of excess selenium is not completely understood. Consumers frequently misuse antioxidant supplements containing selenium in the belief that these will protect them from cancer and other diseases of civilization or just improve their general health. Data from literature have increasingly reported on the inefficacy or even adverse effects of vitamins and trace element supplements on health. The benefits and risks of Se supplements for the prevention of obesity and Type II diabetes are currently the subject of controversial discussion. So, this study was designed to explore the suggestion that selenium and selenoproteins may interfere with the insulin secretion from pancreas and/or insulin signaling in peripheral tissues which may cause insulin resistance and subsequently type 2 diabetes and/or obesity. To achieve this aim the study was conducted on 90 male Wister rats weight (150-200 grams). The rats were divided into 3 groups: Group I (Control group); included 10 healthy male rats. Group II (sodium selenate treated group); this group was subdivided into 4 subgroups (10 rats each) each group was daily orally supplemented with different concentrations of Sodium selenate (5, 10, 50 and 100 $\mu\text{g} / \text{kg}$) for three months. Group III (Selenocysteine treated group); this group was subdivided into 4 subgroups (10 rats each) each group was daily orally supplemented with different concentrations of Selenocysteine (5, 10, 50 and 100 $\mu\text{g} / \text{kg}$) for three months.

After three months the overnight fast animals were scarified and the blood samples were collected and the liver, muscle and white visceral adipose tissues were processed for measurements of lipid profile, serum glucose, insulin level, insulin resistance by HOMA-IR, kidney functions, tissue level of phospho- insulin receptor β subunits (P-IR), tissue level of glucose transporter 4 (Glut4), activity of glutathione peroxidases (GPx) , and tissue level of

selenoprotein P (SeP) . As expected the results of this experimental study indicated that the Se supplementation cause a dose-dependent elevation in the tissues levels of GPx1 activity and SeP. Also, the long-term supplementation of rats with seleno-compounds result significant dose-dependent increase in fasting blood sugar compared to control. This increase in fasting blood glucose is associated with significant dose-dependent decline in fasting insulin level in the rats treated with sodium selenate while those rats treated with selenocysteine showed no significant change in the insulin level compared to untreated rats. There is a dose-dependent increase in HOMA-insulin resistance index in the rats supplemented with Se compounds which indicate an insulin resistance state in these rats that was associated with a dose-dependent decline in the phospho-insulin receptor (active fraction of insulin receptor) and glucose transporter4(Glut4) in the peripheral tissues especially liver and muscle.

The disturbed glucose and insulin homeostasis as a result of long-term supplementation with Se compounds is associated with mild change in the lipid profile. While very mild change in the total cholesterol level was observed with the two Se compounds, only sodium selenate significantly decrease triglycerides level at low dose (10µg/kg) and significantly increase its level at the highest dose (100 µg/kg). Also, the two Se compounds have no significant effects on the LDL-cholesterol but significantly increase the level of HDL-cholesterol which imply a mild or even a good effect of long-term Se supplementation on the lipid profile.

From the results of the present study we can concluded that:

- 1- Long term selenium supplementation is associated with increased risk of type 2 diabetes
- 2- Inorganic selenium (Sodium selenate) is more effective in inducing the diabetic phenotype than organic selenium (selenocysteine)
- 3- Sodium selenate can impair the insulin secretion and insulin sensitivity in liver, skeletal muscle and adipose tissues. While selenocysteine act only on the insulin sensitivity in the peripheral tissues
- 4- Se-dependent glutathione peroxidase and selenoprotein P in the peripheral tissues interfere with the normal insulin signaling and play an important role in the mechanism of diabetes induction by seleno compounds
- 5- The long-term selenium supplementation have mild or even good effects on components of the lipid profile especially HDL-cholesterol level

7. RECOMMENDATIONS

- 1- Selenium must be taken under the supervisions of physicians where the dose not exceeds 400 $\mu\text{g}/\text{day}$.
- 2- It's better that the food which contain selenium must be not taken randomly and we must know the food which containing selenium to management while eating .
- 3- Different drugs which contain selenium must be known to the populations .

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APPENDIX

Serum fasting glucose (mg/dl)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	71	81	132	111	156	77	113	130	137
	85	83	105	108	154	86	107	102	131
	93	84	122	122	223	90	114	100	126
	101	91	123	127	119	103	119	128	149
	81	96	152	136	240	82	100	137	141
	95	82	131	127	148	96	108	132	156
	74	104	129	128	180	77	112	108	148
	94	93	128	126	177	91	121	131	151
	78	78	132	137	166	90	123	130	156
	82	80	130	129	133	93	108	129	132
Mean	85.4	87.20	128.4	125.1	169.6	88.50	112.5	122.7	142.7
SD	9.9	8.42	11.6	9.4	37.7	8.24	7.1	13.7	10.8

Concentration of insulin ($\mu\text{g/ml}$)****Serum**

	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.38	0.27	0.24	0.24	0.30	0.2	0.28	0.22
	0.31	0.22	0.24	0.24	0.31	0.38	0.25	0.26
	0.32	0.30	0.22	0.21	0.27	0.31	0.33	0.27
	0.29	0.33	0.24	0.24	0.35	0.28	0.24	0.3
	0.28	0.33	0.31	0.22	0.32	0.28	0.23	0.26
	0.35	0.34	0.3	0.23	0.33	0.22	0.31	0.29
	0.36	0.26	0.26	0.21	0.34	0.22	0.25	0.22
	0.34	0.37	0.25	0.19	0.27	0.38	0.26	0.28
	0.31	0.31	0.27	0.18	0.27	0.27	0.31	0.22
	0.33	0.32	0.28	0.21	0.28	0.28	0.29	0.27
Mean	0.33	0.31	0.26	0.22	0.30	0.28	0.28	0.26
SD	0.03	0.03	0.03	0.02	0.03	0.06	0.03	0.03

HOMA IR

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.6	1.3	2.1	1.6	2.2	1.3	1.3	2.2	1.8
	1.6	1.5	1.4	1.5	2.2	1.5	2.4	1.5	2.0
	1.8	1.4	1.7	1.6	2.8	1.4	2.1	2.0	2.0
	1.7	1.7	1.8	1.8	1.7	2.1	2.0	1.8	2.7
	1.3	1.8	2.6	2.5	3.1	1.5	1.7	1.9	2.2
	2.0	1.6	2.2	2.3	2.0	1.8	1.4	2.4	2.7
	1.6	1.6	1.7	2.0	2.2	1.5	1.5	1.6	1.9
	1.9	2.0	2.1	1.9	2.0	1.4	2.7	2.0	2.5
	1.4	1.4	2.1	2.2	1.8	1.4	2.0	2.4	2.0
	1.6	1.5	2.0	2.1	1.7	1.5	1.8	2.2	2.1
Mean	1.65	1.58	1.97	1.95	2.17	1.54	1.89	2.0	2.19
SD	0.2	0.21	0.3	0.3	0.5	0.24	0.4	0.3	0.3

Phospho insulin receptor / mg Protein****Liver**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.062	0.062	0.041	0.044	0.041	0.047	0.044	0.051	0.041
	0.051	0.050	0.052	0.041	0.051	0.050	0.051	0.048	0.052
	0.053	0.047	0.044	0.043	0.048	0.051	0.041	0.051	0.051
	0.051	0.052	0.051	0.051	0.038	0.049	0.051	0.052	0.049
	0.049	0.050	0.051	0.048	0.041	0.060	0.048	0.051	0.038
	0.048	0.050	0.053	0.042	0.047	0.050	0.052	0.038	0.041
	0.061	0.057	0.042	0.041	0.042	0.049	0.048	0.044	0.041
	0.058	0.060	0.038	0.048	0.041	0.058	0.042	0.047	0.048
	0.051	0.051	0.054	0.049	0.042	0.060	0.048	0.038	0.051
	0.052	0.049	0.043	0.042	0.047	0.048	0.041	0.048	0.041
Mean	0.054	0.052	0.047	0.045	0.044	0.052	0.047	0.047	0.045
SD	0.005	0.005	0.006	0.004	0.004	0.005	0.004	0.005	0.005

Phospho insulin receptor / mg Protein**** Muscle**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.061	0.057	0.041	0.042	0.037	0.047	0.041	0.061	0.061
	0.059	0.050	0.052	0.041	0.038	0.060	0.051	0.051	0.052
	0.051	0.059	0.042	0.044	0.047	0.049	0.053	0.058	0.051
	0.058	0.061	0.041	0.038	0.052	0.056	0.043	0.048	0.049
	0.049	0.051	0.051	0.047	0.041	0.058	0.048	0.062	0.051
	0.052	0.047	0.042	0.044	0.038	0.050	0.043	0.048	0.043
	0.062	0.059	0.051	0.041	0.044	0.050	0.047	0.052	0.061
	0.051	0.050	0.048	0.048	0.051	0.057	0.051	0.039	0.051
	0.058	0.056	0.045	0.047	0.042	0.060	0.041	0.038	0.053
	0.057	0.058	0.038	0.042	0.041	0.060	0.047	0.051	0.05
Mean	0.056	0.055	0.045	0.043	0.043	0.054	0.047	0.051	0.052
SD	0.005	0.005	0.005	0.003	0.005	0.005	0.004	0.008	0.005

Phospho insulin receptor / mg Protein**** White adipose tissue**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.052	0.063	0.052	0.054	0.051	0.050	0.062	0.054	0.041
	0.051	0.050	0.043	0.041	0.042	0.052	0.054	0.044	0.042
	0.062	0.051	0.051	0.041	0.041	0.062	0.051	0.041	0.042
	0.064	0.051	0.041	0.031	0.048	0.049	0.053	0.042	0.051
	0.051	0.061	0.05	0.041	0.051	0.058	0.051	0.046	0.041
	0.051	0.055	0.054	0.043	0.052	0.050	0.06	0.04	0.05
	0.054	0.060	0.052	0.042	0.041	0.059	0.05	0.048	0.045
	0.058	0.050	0.037	0.051	0.04	0.059	0.048	0.053	0.044
	0.06	0.060	0.041	0.052	0.042	0.060	0.049	0.038	0.038
	0.051	0.059	0.044	0.038	0.05	0.061	0.051	0.052	0.05
Mean	0.055	0.056	0.047	0.043	0.046	0.056	0.053	0.046	0.044
SD	0.005	0.005	0.006	0.007	0.005	0.005	0.005	0.006	0.005

GLU T 4/mg protein**** Muscle**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	4.3	3.1	3	2.3	1.4	3.6	2.7	1.6	1.3
	3.6	3.6	2	2.2	1.6	3.8	3.5	2.9	1.5
	3.3	4.2	1.9	1.7	1.5	4.4	3.9	1.5	1.6
	2.2	2.0	2.3	2.2	1.6	2.4	2.9	1.5	1.4
	2.4	2.2	2.2	1.9	1.7	2.5	3	2.3	1.7
	3.9	3.7	2.5	1.8	1.5	4.2	2.8	1.8	1.8
	2.8	2.6	2	2	1.7	4.3	3.1	1.9	1.4
	4.1	4.0	3.1	2.1	1.6	2.9	3.8	2.8	1.6
	2.8	2.8	2.4	2	1.4	3.1	3.7	2.7	1.4
	2.5	2.4	2.3	2	1.5	2.6	3.5	1.7	1.7
Mean	3.19	3.06	2.37	2.02	1.55	3.38	3.29	2.07	1.54
SD	0.75	0.78	0.41	0.19	0.11	0.78	0.44	0.56	0.16

GLU T4/mg protein**** White adipose tissue**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	3.1	2.6	1.9	1.3	1.7	3.1	2.3	2.2	2.2
	3.1	3.0	2.2	1.8	1.2	2.6	2.8	2.6	3
	2.6	2.3	2.5	1.6	2.1	3	2.3	1.9	3.1
	3.1	3.1	2.2	1.6	2.1	3.2	2	2.4	2.8
	2.7	3.0	2.1	1.7	2.4	2.6	2.1	2	3
	2.5	2.4	2.2	1.9	1.9	2.5	3.1	2.2	3.1
	2.7	2.4	2.4	1.9	1.3	2.7	2.9	2.4	2.9
	2.5	2.7	2	2.1	1.8	2.6	2.7	2.3	2.7
	2.7	2.6	2.3	2.2	2	2.5	3.3	2.5	3
	2.6	2.5	1.9	2	1.5	2.7	3.2	2.4	3.1
Mean	2.76	2.66	2.17	1.81	1.80	2.75	2.67	2.29	2.89
SD	0.25	0.28	0.20	0.27	0.38	0.25	0.47	0.22	0.28

Serum Cholesterol (mg/dl)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	107	103	107	120	112	108	111	110	95
	106	106	97	124	116	113	107	100	116
	112	100	100	110	107	107	113	102	114
	96	105	109	100	102	97	116	104	121
	98	101	143	101	111	98	100	111	118
	101	100	111	108	117	101	111	110	101
	106	99	109	119	123	105	108	103	118
	99	113	98	121	124	106	110	100	116
	105	107	110	123	119	100	118	111	120
	100	108	113	130	117	104	104	108	118
Mean	103.0	104.20	109.7	115.6	114.8	103.90	109.8	105.9	113.7
SD	5.0	4.44	13.0	10.2	6.9	4.95	5.4	4.6	8.6

Serum Triglycerides (mg/dl)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	46	49	65	60	90	41	84	58	43
	77	59	39	35	90	70	70	44	42
	66	62	57	56	83	69	49	58	80
	74	57	60	78	91	71	79	69	77
	51	40	35	65	99	50	67	70	81
	49	39	66	62	91	49	81	61	48
	66	63	41	39	97	70	75	51	47
	71	56	58	60	88	60	55	53	82
	68	64	62	71	87	71	77	67	79
	58	68	37	66	97	53	61	69	80
Mean	62.6	55.70	52.0	59.2	91.3	60.40	69.8	60.0	65.9
SD	10.9	9.98	12.4	13.3	5.0	11.32	11.7	8.9	18.1

Serum High density lipoprotein mg/dl (HDL)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	26	31	37	40	40	28	34	32	30
	32	31	41	40	47	31	38	30	45
	30	28	35	31	38	31	34	33	36
	35	29	31	32	37	33	39	39	41
	31	32	35	37	39	29	34	37	48
	32	36	38	41	41	30	38	34	37
	28	31	43	43	45	34	40	32	43
	33	33	36	38	39	35	32	35	38
	31	28	32	37	40	29	34	41	43
	30	32	37	40	42	27	30	39	49
Mean	30.8	31.10	36.5	37.9	40.8	30.70	35.3	35.2	41.0
SD	2.5	2.42	3.7	3.8	3.1	2.63	3.3	3.6	5.8

Serum low density lipoprotein mg/dl (LDL)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	71.8	71.7	57	68	54	63.0	60.2	66.4	56.4
	58.6	50.0	48.2	77	51	60.0	55	61.2	62.6
	68.8	68.5	53.6	67.8	52.4	51.0	69.2	57.4	62
	46.2	50.1	66	52.4	46.8	60.2	61.2	51.2	64.6
	56.8	56.2	101	51	52.2	56.1	52.6	60	53.8
	59.2	60.2	59.8	54.6	57.8	41.7	56.8	63.8	54.4
	64.8	64.0	57.8	68.2	58.6	63.7	53	60.8	65.6
	51.8	55.0	50.4	71	67.4	58.2	67	54.4	61.6
	60.4	63.2	65.6	71.8	61.6	53.3	68.6	56.6	61.2
	58.4	55.0	68.6	76.8	55.6	66.1	61.8	55.2	53
Mean	59.7	55.15	62.8	65.9	55.7	57.33	60.5	58.7	59.5
SD	7.5	8.84	15.0	9.7	5.9	7.21	6.2	4.6	4.7

Blood urea (mg/dl)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	30.5	31	33.5	27	31.5	33.1	30	28.5	25
	30	33	30	30.5	28.5	33.2	27.5	32	24
	29	29	36.5	31.5	24	29.1	25.5	25	24
	30.5	28	35.5	23.5	27.5	31.0	27.5	33	25.5
	27.5	30.5	32.5	25	25	29.5	29	33.5	26.5
	28.5	32	30.5	28	30.5	28.3	30	33.5	26
	27.5	31.1	29	31.5	29	35.1	25.5	29.5	27.5
	27	28.2	35.5	31.5	24.5	34.9	25.5	33	28
	29	28.0	37	25.5	28.5	27.0	26	26	25.5
	30	31.0	31.5	25	27.5	30.0	28.5	34	27
Mean	28.95	30.18	33.15	27.90	27.65	31.12	27.50	30.80	25.90
SD	1.30	1.78	2.88	3.13	2.51	2.82	1.83	3.33	1.37

Serum Creatinine (mg/dl)

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.4	0.4	0.4	0.4	0.35	0.4	0.35	0.35	0.45
	0.45	0.39	0.3	0.4	0.7	0.46	0.5	0.4	0.75
	0.4	0.35	0.45	0.3	0.45	0.49	0.45	0.4	0.4
	0.5	0.38	0.35	0.45	0.5	0.49	0.35	0.65	0.7
	0.4	0.4	0.4	0.5	0.75	0.38	0.4	0.7	0.65
	0.5	0.4	0.4	0.5	0.45	0.39	0.4	0.45	0.55
	0.45	0.45	0.35	0.4	0.6	0.4	0.55	0.4	0.6
	0.4	0.48	0.45	0.4	0.55	0.38	0.45	0.4	0.4
	0.35	0.49	0.3	0.3	0.4	0.41	0.45	0.6	0.75
	0.45	0.39	0.4	0.35	0.55	0.44	0.35	0.65	0.7
Mean	0.43	0.41	0.38	0.40	0.53	0.42	0.43	0.50	0.60
SD	0.05	0.05	0.05	0.07	0.13	0.43	0.07	0.13	0.14

Total glutathion peroxidase/mg protein****Liver**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	2.9	2.8	2.7	3	2.9	3.2	2.7	2.9	3.8
	2.8	2.9	3.4	2.5	3.2	3.1	2.3	3.1	3.4
	2.8	3.0	2.1	2.9	2.3	2.8	2.8	3.4	3.3
	3.2	2.8	2.2	3.1	3.4	2.8	3.3	3.6	3.4
	2	2.8	3.4	2.2	3.5	3.1	3.2	3	3.2
	3.1	2.0	2.6	3	3.7	3.3	2.6	3	3.4
	2.7	3.1	3.2	2.6	3.9	3.3	2.9	3.3	3.7
	2.7	3.2	3.1	3.1	4	3.1	2.9	3.3	3.5
	3	2.9	2.8	3.7	3.5	3.0	3.1	3.2	3.9
	3.1	2.9	2.9	2.5	3	3.0	2.5	3.2	3.3
Mean	2.83	2.84	2.84	2.86	3.34	3.07	2.83	3.20	3.49
SD	0.34	0.32	0.46	0.42	0.51	0.18	0.32	0.21	0.23

Total glutathion peroxidase/mg protein**** Muscle**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	2.8	2.6	2.6	3.4	3.7	2.6	2.6	4.4	3.7
	2.7	2.7	3.2	2.8	3.7	2.5	3.3	3.8	4.1
	3.2	2.4	2.1	2.1	4.3	2.7	3.4	3.5	4.2
	2	2.5	2.6	2.8	3.5	2.6	3	2.9	4.8
	2.7	3.0	3.8	2.8	3.6	2.8	3.2	3.3	4.2
	2.6	2.8	2.5	3.3	3.5	2.8	2.8	4.1	3.9
	2.5	2.9	3	2.9	4	2.9	3.1	3.9	3.3
	2.6	3.2	2.4	2.9	4.2	3.3	3.4	3.6	4
	2.4	2.8	2.5	3	3.8	2.9	3.4	3	4.6
	2.5	3.0	3.7	3.1	3.9	3.0	2.8	3.5	4.4
Mean	2.60	2.79	2.84	2.91	3.82	2.81	3.10	3.60	4.12
SD	0.31	0.25	0.57	0.35	0.28	0.23	0.29	0.47	0.43

Total glutathion peroxidase/mg protein**** White adipose tissue**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	2.8	3.3	4.3	4.3	4	3.4	3.7	3.5	4.9
	2.9	3.0	3.5	3.5	4	2.9	3.2	3.6	4.9
	2.7	2.9	3.7	3.7	4.1	3.0	3.7	3.6	4.7
	3.4	3.3	3.3	3.4	4	3.4	3.5	3.6	4.1
	2.4	3.0	2.8	3	3.7	2.9	3.8	4.2	3.6
	2.9	2.5	3.9	3.9	4.5	2.5	3.9	4.2	4.7
	3.3	3.5	3.8	3.8	4.1	3.6	3.8	3.4	4.9
	2.8	2.8	3.8	4.1	3.9	2.8	3.9	4.1	4.8
	2.9	2.9	3.7	3.4	3	3.0	3.9	3.5	4.5
	3.2	2.9	3.9	3.5	4.1	2.9	4.1	4.3	4.5
Mean	2.93	3.01	3.67	3.66	3.94	304	3.75	3.80	4.56
SD	0.30	0.29	0.40	0.38	0.39	0.33	0.25	0.35	0.42

Glutathione peroxidase/mg protein (Selenium dependent)****Liver**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.7	1.7	2	1.5	2.5	1.6	1.9	1.8	3
	1.8	1.9	2.6	2.3	1.5	1.8	1.8	2.2	2.3
	2.2	1.7	1.6	1.9	1.9	2.3	2	2.6	2
	1.6	1.9	1.4	2.2	3	1.9	2.1	2.8	2.9
	1.5	2.1	1.7	1.5	2	1.7	2.4	2.6	2.7
	2	1.6	2.2	2	2.2	2.1	2	2	2.8
	1.8	2.4	1.7	1.6	2.4	1.9	2.1	2.5	2.7
	1.7	1.9	1.9	1.8	2.8	1.8	2.2	2.4	3
	1.8	2.0	1.8	2.4	3.1	1.7	2	2.5	2.9
	1.6	1.8	1.5	1.6	2	1.7	1.7	2.1	2.5
Mean	1.77	1.90	1.84	1.88	2.34	1.85	2.02	2.35	2.68
SD	0.21	0.23	0.36	0.34	0.52	0.21	0.20	0.31	0.33

Glutathione peroxidase/mg protein (Selenium dependent)**** Muscle**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.7	1.7	1.6	1.7	1.8	2.2	1.8	2.9	3.2
	1.6	1.5	1.6	2	2.5	1.6	2.8	2.9	3
	1.6	2.0	1.7	1.7	2.4	1.7	1.9	2.5	3.5
	1.5	1.6	2.1	2.4	3	1.6	2.5	2.4	4.2
	2.2	1.6	2.4	1.8	2.7	1.7	2.7	2.2	3.3
	1.6	2.2	1.8	1.9	1.9	1.6	1.6	2.2	3.1
	1.5	1.5	1.7	2	2.4	1.7	2.5	2.7	3
	2	1.6	2	1.6	2.1	1.9	2	2.8	3.4
	1.5	1.7	1.6	2.2	2.1	1.5	2.3	2.4	3.8
	1.6	1.9	2.1	1.5	2.3	1.6	1.9	2.8	3.7
Mean	1.68	1.73	1.86	1.88	2.32	1.71	2.20	2.58	3.42
SD	0.23	0.23	0.28	0.28	0.36	0.20	0.41	0.27	0.39

Glutathione peroxidase/mg protein (Selenium dependent)**** White adipose tissue**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.1	2.0	3	3.7	2.3	1.9	3.1	3.1	4
	1.4	1.8	3	2.3	2.4	1.7	2.7	3	4
	1.6	1.7	3.2	3.2	3.5	1.8	3.2	3.2	4.1
	1.7	1.4	2.9	2.4	2.8	1.3	3	3	3.6
	1.9	1.3	1.7	2	2.6	1.5	3.3	2.8	3.1
	1.2	1.9	3.1	2.8	3.3	1.4	3.1	3.7	4
	1.3	1.8	3.2	3.3	2.8	1.6	3.2	2.9	4.1
	1.6	1.6	3	2.9	2.7	1.6	3.1	3	4.3
	1.6	1.4	2.9	2.7	2.5	1.8	3.3	2.9	3.9
	1.8	1.1	2.8	3	3.1	1.9	3.3	3.1	3.8
Mean	1.52	1.60	2.88	2.83	2.80	1.65	3.13	3.07	3.89
SD	0.26	0.29	0.43	0.51	0.39	0.21	0.18	0.25	0.33

Glutathion peroxidase /mg protein(non-selenium dependent)

**Liver

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.2	1.1	0.7	1.5	0.4	1.6	0.8	1.1	0.8
	1	1.0	0.8	0.2	1.7	1.3	0.5	0.9	1.1
	0.6	1.3	0.5	1	0.4	0.5	0.8	0.8	1.3
	1.6	0.9	0.8	0.9	0.4	0.9	1.2	0.8	0.5
	0.5	0.7	1.7	0.7	1.5	1.6	0.8	0.4	0.5
	1.1	0.4	0.4	1	1.5	1.0	0.6	1	0.6
	0.9	0.7	1.5	1	1.5	1.4	0.8	0.8	1
	1	1.3	1.2	1.3	1.2	1.2	0.7	0.9	0.5
	1.2	0.9	1	1.3	0.4	1.3	1.1	0.7	1
	1.5	1.1	1.4	0.9	1	1.4	0.8	1.1	0.8
Mean	1.06	0.94	1.00	0.98	1.00	1.22	0.81	0.85	0.81
SD	0.35	0.28	0.44	0.36	0.55	0.34	0.21	0.21	0.28

Glutathion peroxidase /mg protein(non-selenium dependent)**** Muscle**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.1	0.9	1	1.7	1.9	0.3	0.8	1.5	0.5
	1.1	1.2	1.6	0.8	1.2	0.8	0.5	0.9	1.1
	1.6	0.4	0.4	0.4	1.9	0.9	1.5	1	0.7
	0.5	0.9	0.5	0.4	0.5	0.9	0.5	0.5	0.6
	0.5	1.4	1.4	1	0.9	1.0	0.5	1.1	0.9
	1	0.6	0.7	1.4	1.6	1.0	1.2	1.9	0.8
	1	1.4	1.3	0.9	1.6	1.1	0.6	1.2	0.3
	0.6	1.6	0.4	1.3	2.1	1.3	1.4	0.8	0.6
	0.9	1.1	0.9	0.8	1.7	1.3	1.1	0.6	0.8
	0.9	1.1	1.6	1.6	1.6	1.3	0.9	0.7	0.7
Mean	0.92	1.06	0.98	1.03	1.50	0.99	0.90	1.02	0.70
SD	0.33	0.37	0.48	0.46	0.49	0.30	0.38	0.43	0.22

Glutathion peroxidase /mg protein(non-selenium dependent)**** White adipose tissue**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	1.7	1.3	1.3	0.6	1.7	1.5	0.6	0.4	0.9
	1.5	1.2	0.5	1.2	1.6	1.2	0.5	0.6	0.9
	1.1	1.2	0.5	0.5	0.6	1.2	0.5	0.4	0.6
	1.7	1.9	0.4	1	1.2	2.1	0.5	0.6	0.5
	0.5	1.7	1.1	1	1.1	1.0	0.5	1.4	0.5
	1.7	0.6	0.8	1.1	1.2	1.1	0.8	0.5	0.7
	2	1.7	0.6	0.5	1.3	2.0	0.6	0.5	0.8
	1.2	1.2	0.8	1.2	1.2	1.2	0.8	1.1	0.5
	1.3	1.5	0.8	0.7	0.5	1.2	0.6	0.6	0.6
	1.4	1.8	1.1	0.5	1	1.0	0.8	1.2	0.7
Mean	1.41	1.41	0.79	0.83	1.14	1.35	0.62	0.73	0.67
SD	0.42	0.39	0.30	0.30	0.38	0.40	0.13	0.36	0.16

Selenoprotein/mg Protein**** Liver**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.22	0.23	0.23	0.22	0.21	0.22	0.33	0.31	0.49
	0.31	0.31	0.25	0.31	0.44	0.30	0.22	0.41	0.32
	0.31	0.32	0.21	0.32	0.42	0.33	0.28	0.35	0.33
	0.21	0.22	0.24	0.33	0.41	0.22	0.31	0.33	0.39
	0.31	0.33	0.23	0.41	0.38	0.31	0.33	0.31	0.42
	0.31	0.31	0.23	0.29	0.44	0.32	0.31	0.41	0.41
	0.21	0.21	0.24	0.33	0.31	0.23	0.28	0.32	0.48
	0.21	0.22	0.23	0.31	0.32	0.23	0.21	0.31	0.51
	0.22	0.24	0.33	0.36	0.38	0.24	0.27	0.31	0.44
	0.22	0.23	0.24	0.31	0.31	0.23	0.29	0.41	0.51
Mean	0.25	0.26	0.24	0.32	0.36	0.26	0.28	0.35	0.43
SD	0.05	0.05	0.03	0.05	0.07	0.05	0.04	0.05	0.07

Selenoprotein/mg Protein**** Muscle**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.11	0.31	0.37	0.28	0.31	0.40	0.33	0.31	0.41
	0.22	0.28	0.33	0.31	0.33	0.34	0.23	0.31	0.33
	0.24	0.18	0.39	0.33	0.28	0.25	0.31	0.4	0.31
	0.33	0.27	0.24	0.21	0.41	0.23	0.33	0.42	0.41
	0.38	0.35	0.31	0.38	0.33	0.11	0.31	0.33	0.51
	0.31	0.30	0.21	0.35	0.35	0.33	0.28	0.42	0.41
	0.31	0.39	0.22	0.31	0.39	0.32	0.31	0.31	0.42
	0.41	0.38	0.31	0.28	0.32	0.43	0.31	0.28	0.31
	0.18	0.16	0.21	0.3	0.31	0.19	0.22	0.4	0.32
	0.24	0.21	0.31	0.3	0.3	0.26	0.31	0.41	0.42
Mean	0.27	0.28	0.29	0.31	0.33	0.29	0.29	0.36	0.39
SD	0.09	0.08	0.07	0.05	0.04	0.09	0.04	0.06	0.07

Selenoprotein/mg Protein**** White adipose tissue**

	Control	Sodium selenate 5 ug/kg	Sodium selenate 10 ug/kg	Sodium selenate 50 ug/kg	Sodium selenate 100 ug/kg	Selenocysteine 5 ug/kg	Selenocysteine 10 ug/kg	Selenocysteine 50 ug/kg	Selenocysteine 100 ug/kg
	0.11	0.31	0.22	0.44	0.33	0.32	0.36	0.31	0.36
	0.32	0.35	0.51	0.41	0.41	0.33	0.28	0.42	0.35
	0.32	0.33	0.31	0.48	0.51	0.32	0.31	0.41	0.4
	0.33	0.33	0.32	0.41	0.62	0.34	0.33	0.4	0.44
	0.3	0.13	0.43	0.51	0.6	0.11	0.29	0.45	0.41
	0.31	0.31	0.41	0.48	0.38	0.32	0.34	0.32	0.41
	0.22	0.31	0.42	0.52	0.41	0.23	0.33	0.4	0.38
	0.22	0.24	0.33	0.41	0.61	0.22	0.31	0.4	0.37
	0.31	0.22	0.51	0.51	0.52	0.31	0.27	0.28	0.41
	0.33	0.35	0.41	0.41	0.51	0.34	0.28	0.33	0.4
Mean	0.28	0.29	0.39	0.46	0.49	0.28	0.31	0.37	0.39
SD	0.07	0.07	0.09	0.05	0.10	0.07	0.03	0.06	0.03

الملخص العربي

النوع ٢ من داء السكري هو اضطراب التمثيل الغذائي الذي يتميز بارتفاع السكر في الدم الناتج عن إفراز الأنسولين بشكل غير صحيح . على مدى ٥٠ عاما الماضية فإن مرض السكر ينمو بسرعة. وكان انتشاره في جميع أنحاء العالم تقدر بين البالغين ب ٢٨٥ مليون (٦.٤٪) في عام ٢٠١٠، ومن المتوقع أن تزيد هذه القيمة إلى حوالي ٤٣٩ مليون (٧.٧٪) بحلول عام ٢٠٣٠ وسوف تكون مصر في المرتبة العاشرة من دول العالم حيث أن لديها أكبر عدد الأشخاص الذين يعانون من مرض السكري، مما يجعلها واحدة من أخطر الأمراض. وقد أدى الربط المتكرر بين مرض السكري والسمنة أن البدانة ومقاومة الأنسولين المرتبطة قد تكون مسؤولة عن حدوث ما يصل إلى ٩٠٪ من داء السكري من النوع ٢. وحيث أن العضلات والهيكل العظمي هو نسيج الأيضي الرئيسي، وهو ما يمثل حوالي ٨٠٪ من مجموع استخدام الجلوكوز في ظل ظروف حفز الأنسولين، وأيضا الأنسجة الدهنية والكبد لهما دورا هاما في توازن الجلوكوز، فإن عدم عمل الأنسولين في هذه الأنسجة الرئيسية قد تكون السبب في حدوث النوع الثاني من مرض السكري.

ومن بين العناصر المؤثرة الضرورية لصحة الإنسان السيلينيوم الفريد في تركيبه الكيميائي الحيوي ، و كذلك له القدرة المضادة للأكسدة. ومن المتوقع أن يكون له تأثير في مكافحة السكري و كشفت الدراسات الأخيرة وجود ارتباط بين مستويات السيلينيوم العاليه في البلازما والسكري من النوع ٢. وما زالت الية تأثير السيلينيوم على إحداث السكري غير مفهومه حتى الآن .

كثير من المرضى يسيؤون استخدام المكملات الغذائية المضاده للأكسده المحتويه على السيلينيوم لإعتقادهم أنه سوف يحميهم من السرطان والأمراض العصريه الأخرى أو لمجرد تحسين صحتهم العامة. في حين ان المكملات الغذائية المحتويه على السيلينيوم للوقايه من السمنه ومرض السكري من النوع الثاني هي موضع نقاش مثير للجدل ،لذلك تم تصميم هذه الدراسه لاستكشاف دور السيلينيوم في التداخل مع افراز الانسولين من البنكرياس او من الأنسجة الأخرى مع دراسة الإشارات التي قد تسبب مقاومة الأنسولين ومرض السكري من النوع الثاني او السمنه .

لتحقيق هذا الهدف أجريت الدراسة على ٩٠ من ذكور الفئران (ويستر) ووزنها (١٥٠-٢٠٠ غرام). تم تقسيم الفئران إلى ٣ مجموعات: المجموعة الأولى (مجموعة الفئران الأصحاء)؛ شملت ١٠ ذكور من الفئران الأصحاء. المجموعة الثانية (مجموعة سيلينات الصوديوم)؛ وقد تم تقسيم هذه المجموعة إلى ٤ مجموعات فرعية (١٠ فئران لكل منها) وأعطيت كل مجموعة يوميا عن طريق الفم تركيزات مختلفة من سيلينات الصوديوم (٥ و ١٠ و ٥٠ و ١٠٠ ميكروغرام / كجم) لمدة ثلاثة أشهر. المجموعة الثالثة (مجموعة السيلينوسيسيتين)؛ وقد تم تقسيم هذه المجموعة إلى ٤ مجموعات فرعية (١٠ فئران لكل منها) وأعطيت كل مجموعة يوميا عن طريق الفم تركيزات مختلفة من سيلينوسيسيتين (٥ و ١٠ و ٥٠ و ١٠٠ ميكروغرام / كجم) لمدة ثلاثة أشهر. بعد ثلاثة أشهر تم ذبح الفئران وتم جمع عينات الدم وتم استئصال الكبد والعضلات والأنسجة الدهنية لقياس الدهون ، والجلوكوز في الدم، ومستوى الأنسولين، ومقاومة الأنسولين بواسطة IR-HOMA، وظائف الكلى ومستوى الأنسجة من مستقبلات β للأنسولين المفسره (phosphor insulin receptor β subunit) ومستوى الأنسجة من ناقل الجلوكوز ٤ (GLUT4)، نشاط الجلوتاثيون بيروكسيدازات ، ومستوى الأنسجة من selenoprotein P .

أشارت نتائج هذه الدراسة التجريبية أن مكملات السيلينيوم تسبب ارتفاع معتمد على الجرعة في مستويات الأنسجة من (GPX-1) و selenoprotein . وأيضا، فإن مركبات سيلينات الصوديوم قد أدت الى زيادة كبيرة في نسبة السكر في الدم معتمده على نسبة الجرعه ويرتبط هذا الارتفاع في السكر في الدم مع انخفاض في مستوى الانسولين في الفئران المعطاه لسيلينات الصوديوم في حين لم تظهر الفئران المعامله مع سيلينوسيسيتين أي تغيير ملموس في مستوى الأنسولين مقارنة مع المجموعه الضابطه. ووجد زيادة معتمده على الجرعة في مؤشر مقاومة HOMA على الأنسولين مع انخفاض في مستقبلات الأنسولين (جزء النشاط لمستقبلات الأنسولين) وناقل الجلوكوز ٤ (GLUT4) في الأنسجة الطرفية وخاصة الكبد والعضلات.

الخلل في الجلوكوز وتوازن الأنسولين كان كنتيجة لمكملات السيلينيوم لمدته طويله مع تغيير طفيف في مستوى الدهون. في حين ظهر تغيير معتدل في مستوى الكوليسترول الكلي في كلا المجموعتين (sodium selenate and selenocystine)، ووجد أن سيلينات الصوديوم تقلل كثيرا من مستوى الدهون الثلاثية في جرعة منخفضة (١٠ $\mu\text{g/kg}$) وزيادة كبيرة مع الجرعة (١٠٠ ميكروغرام / كغ).

من نتائج هذه الدراسة يمكننا استنتاج ما يلي:

١. يرتبط مكملات السيلينيوم طويلة الأجل مع زيادة خطر داء السكري من النوع ٢.
٢ - (سيلينات الصوديوم) هي أكثر فاعليه في إحداث النمط الظاهري لداء السكري من (سيلينوسيسين). .

٣- يمكن لسيلينات الصوديوم ان تضعف افراز الانسولين والحساسية للانسولين في الكبد والعضلات والهيكل العظمي والأنسجة الدهنية. بينما سيلينوسيسين تعمل فقط على حساسية الأنسولين في الأنسجة الطرفية .

٤- الجلوتاثيون بيروكسيداز و selenoprotein P في الأنسجة الطرفية تتداخل مع إشارات الانسولين وتلعب دورا هاما في آلية تحريض السكري بواسطة مركبات السيلينيوم .

٥- مكملات السيلينيوم طويلة الأجل لها آثار خفيفة أو حتى جيدة على مكونات الدهون وخاصة مستوى الكوليسترول HDL-

تقييم دور السيلينيوم المكمل فى آلية حدوث مرض السكرى من النوع الثانى

رسالة

مقدمة إلى معهد البحوث الطبية- جامعة الإسكندرية
ايفاء جزئيا لشروط الحصول على درجة

الدكتوراه

فى

الكيمياء الحيوية

مقدمة من

أحمد الصادق عبد الغنى النجار

بكالوريوس علوم (حيوان وكيمياء)- كلية العلوم- جامعة المنصورة- ١٩٩٦
ماجستير فى الكيمياء الطبية التطبيقية- معهد البحوث الطبية- جامعة الإسكندرية- ٢٠٠٧

معهد البحوث الطبية

جامعة الإسكندرية

٢٠١٥

تقييم دور السيلينيوم المكمل فى آلية حدوث مرض السكرى من النوع الثانى

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للحصول على درجة

الدكتوراه

فى
الكيمياء الحيوية

موافقون

لجنة المناقشة والحكم على الرسالة

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